DR. SHAH'S CLINICAL

For PGs, IMM, FCPS-II Medicine Clinicals & MD

Long & Short Cases

* Extensive Coverage of long and short cases
* Relevant Differential Diagnoses (D/Ds)
* CARE/RECA Frameworks
* Illustrated Tables
* Investigations and Treatment
* Recent advances in Medicine

By:

Dr. Syed Yar Muhammad Shah
MBBS, FCPS, (Medicine)
Consultant Physician

Co-Author

Dr. Syed Yasir Hussain Gilani
Associate Professor of Medicine
ATH -Abbottabad

PRINCE
BOOK HOUSE
MBBS Books, DPT, Nursing Books, CSS PMS Books, Novels & General Books, Stationery & Medical Equipments Availabe here.
NOTE: PDF FILE Convert to Copy Print Facilities Available
Peshawar Shop: Arbab Road, Peshawar Saddar.
0333-9111926 / 0333-9291862
Mardan Shop: Mardan City Center Shop No.3-4 Opp OPD Gate Mardan Medical Complex Mardan

Scanned with CamScanner

Table of Contents

APPROACH TO SHORTNESS OF BREATH 10
APPROACH TO SOB (Due to COPD) 13
VIVA OF COPD 18
APPROACH TO SOB (Due to Asthma) 28
VIVA OF ASTHMA 31
APPROACH TO ALLERGIC BRONCHOPULMONARY ASPERGILLOSIS 38
APPROACH TO BLOOD IN THE SPUTUM (Due to CA Lung) 41
VIVA OF CA LUNG 45
APPROACH TO DRY COUGH (Due to DPLD esp. ILD) 50
APPROACH TO PRODUCTIVE COUGH (Due to Bronchiectasis) 59
VIVA OF BRONCHIECTASIS 63
CYSTIC FIBROSIS (CF) 67
APPROACH TO BLOOD IN SPUTUM (Due to Pulmonary TB) 70
VIVA OF TUBERCULOSIS 73
LATENT TUBERCULOSIS 88
APPROACH TO WORSENING OF SHORTNESS OF BREATH (Due to Heart Failure) 92
APPROACH TO FEVER OF UNKNOWN ORIGIN (Infective endocarditis) 105
VIVA OF Infective Endocarditis 108
APPROACH TO PALPITATION (Rheumatic Heart Disease) 113
APPROACH TO BLOOD IN VOMITUS Upper GI Bleed Due To Chronic Liver disease 120
HEPATITIS C 130
VIVA OF HEPATITIS B 141
APPROACH TO JAUNDICE 150
APPROACH TO ABDOMINAL DISTENSION (Due to CLD) 152
APPROACH TO PER RECTAL BLEED (As case of IBD) 176
APPROACH TO CHRONIC DIARRHEA (AS A CASE OF HIV) 190
HIV Infection and AIDS 202
PANCREATIC PATHOLOGIES IN MEDICINE 225
CHRONIC PANCREATITIS 235
AUTOIMMUNE PANCREATITIS (AIP) 245
PANCREATIC ADENOCARCINOMA 249
APPROACH TO DECREASED URINE OUTPUT (Due to CKD) 257

Scanned with CamScanner

APPROACH TO PEDAL OEDEM (Due to CKD) 259
APPROACH TO VOMITING (Due to CKD) 260
APPROACH TO BLOOD IN URINE (Due to CKD) 262
APPROACH TO ALTERED SENSORIUM (Due to CKD) 262
VIVA of CKD 264
APPROACH TO POLYURIA (Due to DM) 274
APPROACH TO NUMBNESS OF HANDS & FEET (Due to DM) 275
APPROACH TO FOOT ULCER (Due to DM) 276
APPROACH TO UNCONTROLLED BLOOD SUGAR 277
VIVA OF DIABETES 279
APPROACH TO PALPITATION (Due to Hyperthyroidism) 296
APPROACH TO NECK SWELLING (Due to Hyperthyroidism) 298
VIVA OF HYPERTHYROIDISM 300
HYPOTHYROIDISM 307
VIVA OF HYPOTHYROIDISM 308
APPROACH TO WEIGHT GAIN (Due to Cushing syndrome) 313
VIVA OF CUSHING SYNDROME 316
APPROACH TO HEADACHE (Due to Acromegaly) 325
VIVA OF ACROMEGALY 327
APPROACH TO HYPERTENSION 329
APPROACH TO UNCONTROLLED HYPERTENSION (Due to Pheochromocytoma) 330
VIVA OF HYPERTENSION 333
APPROACH TO JOINTS PAIN (RA & SLE) 337
VIVA of RA 342
VIVA OF SLE 351
VIVA OF ANKYLOSING SPONDYLITIS 365
APPROACH TO SKIN TIGHTNESS (Due to systemic sclerosis) 372
VIVA OF SYSTEMIC SCLEROSIS 374
APPROACH TO MUSCLE WEAKNESS (Due to Dermatomyositis and polymyositis) 378
VIVA OF DERMATOMYOSITIS (DM) & POLYMYOSITIS (PM) 380
VASCULITIS 385
APPROACH TO FATIGABILITY (Due to anemia) 397
VIVA OF ANEMIA 399

Scanned with CamScanner

IRON DEFICIENCY ANEMIA (IDA) 401
THALASSEMIA 403
APPROACH TO LUMPS AND BUMPS (Due to Lymphoma) 416
VIVA OF LYMPHOMA 418
APPROACH TO MASS/HEAVINESS IN LEFT HYPOCHONDRIUM (Due to CML/CLL) 425
VIVA Chronic Myeloid Leukemia 426
ACUTE MYELOID LEUKAEMIA (AML) 432
ACUTE LYMPHOBLASTIC LEUKAEMIA (ALL) 435
Myelodysplastic Syndromes (MDS) 442
Multiple Myeloma (MM) 446
APPROACH TO VARIOUS PRESENTATIONS OF IDIOPATHIC THROMBOCYTOPENIC PURPURA (ITP) 450
VIVA OF STROKE 461
APPROACH TO PARAPLEGIA/PARAPARESIS (Flaccid and Spastic) 470
VIVA of GBS 472
Spastic Paraparesis/paralysis due to TM 480
CIDP 485
MYASTHENIA GRAVIS 490
VIVA OF MYASTHENIA GRAVIS 493
APPROACH TO TREMORS (Due to Parkinsonism) 498
VIVA PARKINSONISM: 500
APPROACH TO ALTERED SENSORIUM (Due to seizure) 504
SIDE EFFECTS OF ANTIEPILEPTIC MEDICATIONS: 507
STATUS EPILEPTICUS 511
Demyelinating CNS Disorders: 513
TUBERCULOUS MENINGITIS: 516
Cauda Equina Syndrome and Connus Medullaris Syndrome 521
MOTOR NEURON DISEASE 524
IMPORTANT SHORT CASES 528
Cardiology 528
MITRAL STENOSIS (MS) 530
MITRAL REGURGITATION (MR) 536
MITRAL VALVE PROLAPSE (MVP) 540

Scanned with CamScanner

PROSTHETIC MITRAL VALVE 54
AORTIC STENOSIS 54
AORTIC REGURGITATION 54
VENTRICULAR SEPTAL DEFECT (VSD) 55
Approach for Long Case 56
ATRIAL SEPTAL DEFECT (ASD) 56
HYPERTROPHIC OBSTRUCTIVE CARDIOMYOPATHY (HOCM) 56
PULMONARY STENOSIS 57
IMPORTANT NEUROLOGY SHORT CASES 57
SPEECH 57
GAIT 57
STROKE 58
MULTIPLE SCLEROSIS 58
MOVEMENT DISORDERS AND PARKINSON'S DISEASE 59
ATAXIA AND CEREBELLAR SYNDROMES 60
BRAIN STEM SYNDROME 60
MOTOR NEURON DISEASE 60
GUILLIAN BARRE SYNDROME: 61
CHRONIC INFLAMMATORY DEMYELINATING POLYNEUROPATHY 61
MYASTHENIA GRAVIS 62
MUSCULAR DYSTROPHY 62
CRANIAL NERVE PALSIES 62
TROCHLEAR NERVE PALSY (4th Cranial Nerve) 63
ABDUCENT NERVE PALSY (6TH CRANIAL NERVE PALSY) 63
7TH CRANIAL NERVE PALSY (FACIAL NERVE) 63
NERVE PALSIES OF THE UPPER LIMB 64
CEREBELLOPONTINE ANGLE TUMOUR: (CP angle Tumor) 64
RHEUMATOLOGY SHORT CASES SCHEMES 65
LONG CASE SCHEME OF RHEUMATOLOGY CASE : 65

Scanned with CamScanner

RESPIRATORY SYSTEM

APPROACH TO SHORTNESS OF BREATH

Few imp D/D's of acute shortness of breath

- **less likely to encounter such patients in exam**

1. Cardiac Causes

- Acute MI(cardiogenic shock)
- Acute Pulmonary Edema
- Acute Valvular Insufficiency
- Acute Aortic Dissection(a young gentleman diagnosed case of Marfan syndrome once was a long case in Islamabad centre
- Acute Pericardial Tamponade

2. Respiratory Causes

- Pneumothorax
- Acute Pulmonary Embolism
- Inhale Foreign Body (may cause lobar collapse
- Acute Asthma (previously undiagnosed
- Acute Exacerbation of COPD(previously undiagnosed
- ARDS
- Acute Massive Pleural Effusion

3 Miscellanies

Metabolic Acidosis like DKA and lactic acidosis etc.

Anaphylaxis

Psychogenic hyperventilation

Important D/D, s of chronic shortness of breath and their description

Likely to encounter such patients in CPSP exam

1 cardiac Causes

- **CCF** →Hx of SOB, pink frothy sputum, distended neck veins and gen body swelling.
- **Valvular heart disease**
  - Rheumatic heart disease
    - HX of monthly intramuscular injection, abnormal movement of any part of body
  - Non- Rheumatic heart disease
  - Congenital
- Cardiomyopathies
  - **Dilated cardiomyopathy**

HX of alcohol abuse, chemo (doxorubicin) and radiation exposure etc.

- **Restrictive cardiomyopathy**

Past /Contact HX of TB (low grade fever weight loss, night time sweating with often blood stain

Scanned with CamScanner

sputum

- **Hypertrophic Cardiomyopathy**

HX of sudden cardiac death in family

- **Ischemic heart Disease**

HX of smoking, DM, HTN, lipids disorders, sedentary lifestyle.

- **Infective endocarditis**

HX of IV drug abuse, recent instrumentation of the body &surgery, tooth extraction, high risk sexual behaviour etc.

2 RESPIRATORY CAUSES

- **Asthma**

  HX of SOB with dry cough that is worse in the late night & early morning e.g. diurnal variation and associated with wheezy chest sounds

- **COPD**

  HX of SOB with productive cough that is worse during the winter season on the background of chronic smoking or biomass exposure

- **Pneumonia**

  HX of high-grade fever, rigors and chills with rusty sputum

- **Pulmonary TB**

HX of low-grade fever, night sweats, weight loss and productive cough that is sometime stain with blood

- **BRONCHIECTASIS**

  HX of copious amount of foul smelling sputum that is worse during the morning and at certain position

- **ILD**

  Hx of SOB and dry cough and past Hx of exposure to factory, particles, fumes, farm , dusts ,drugs & radiation or known case of connective tissue disorder.

- **PLEURAL EFFUSION**

Hx of collection or drainage of fluid from chest cavity

- **Cor Pulmonale**

  Hx of some lung pathology, now presented with lower limbs & abdominal swelling, prominent neck veins and tender right hypochondrium (congestive hepatomegaly)

- **SARCOIDOSIS**

  Painful skin lesion on shin

- **CA LUNG**

  Hx of weight loss, decrease appetite, change in the quality of voice (hoarseness), difficulty in swallowing and lumps and bumps in the body.

3. AUTOIMMUNE DISORDERS

- **Connective tissue disorders and vasculitis**

  A general description

Scanned with CamScanner

Hx of oral ulcers, photosensitivity, hair fall, arthralgia or arthritis, (palpable or) petechial skin rash and blood in sputum or urine plus constitutional symptoms.

4 Anemia

Hx of SOB associated with Change in the complexion, palmar and conjunctival pallor, racing of heartbeats and easy fatigability that is non-fluctuating.

5 CKD

Hx of decrease urine output, blood in the urine or frothy urine and patient is on renal replacement therapy.

6 CLD

Hx of blood in the vomitus, black tarry fouls smelling stools and abdominal distension +_ yellow discoloration of sclera.

7 Thyroid Disorder (Hypo/Hyper)

Hx of associated with heat intolerance, excessive sweating, involuntary movements of hands, loose motions and irritability +_ swelling in the neck.

Hx of cold intolerance, weight gain, periorbital puffiness, sluggish mental activities, dry rough skin and hair +_ swelling in the neck

8 Neuromuscular Disorder

MG, MND, GBS etc.

Hx of fluctuating weakness that is more at the end of the day associated with double vision or regurgitation of foods and difficulty in swallowing.

9 Recurrent thromboembolism

Hx of prolong embolization, recent travel, family Hx of lower limb swelling (DVT due to hypercoagulable state

Scanned with CamScanner

APPROACH TO SOB (Due to COPD)

Presenting complaints

(1) Worsening of shortness of breath… 7 day or

(2) Cough

HOPI (& ODPARAV)

MY patient XYZ normotensive ,normoglycemic ,chronic smoker for 30 years ,having recurrent shortness of breath over the past years '' now presented with worsening of shortness of breath for the last 7 days.

- Old-aged examiners famously known as babas do not like to listen premorbid like diabetic or hypertensive /normotensive, norm glycaemic or any condition in the beginning of HOPI while young examiners do.

Shortness of breath started gradually and is progressive in nature .Initially, the patient experienced shortness of breath on moderate exertion like, on climbing stair; however fort the last one-week patient became short of breath even on walking few steps on the plain ground. This shortness of breath was aggravated by exertion & lying flat on the bed therefore my patient use 2 pillows to prop-up himself. Initially SOB was relived with use of inhaler ,however now for the last 7 days despite using inhaler patient remained short of breath throughout the day and night .it is worth mentioning that his inhaler technique is correct. Shortness of breath is associated with cough with scanty sputum production that is non- purulent having no blood and is more at night. It is also associated with chest tightness and wheezy chest sounds. There is also associated history of seasonal variation of these symptoms in the winter and HX of skin allergies .However there is no associated history of …

Now exclude few important relevant DDs of shortness of breath (CPSP examiners expect you to rule out important DDs of each disease like COPD here even if you are 200% sure that this is the case of COPD.

- **Bronchial Asthma** →There is No HX of SOB & dry cough with diurnal variation that is associated with wheezy chest sounds & Hx of atopy and family history of asthma

- **Pneumonia** →There is no HX of high-grade fever, rigors and chills with rusty sputum
- **Pulmonary TB** There is no HX of low grade fever , night sweats, weight loss and productive cough that is sometime stain with blood
- ***Bronchiectasis***→ There is no HX of copious amount of foul smelling sputum that is worse in the morning and expectorate at certain position
- **ILD** →There is no Hx of SOB and dry cough with past Hx of exposure to factory, particles, fumes, farm, dusts, drugs & radiation or known case of connective tissue disorder .
- **Pleural Effusion** →There is no Hx of fluid collection in chest cavity
- **Cor Pulmonale**→ There is no Hx of prominent neck veins , tender right hypochondrium and lower limb swelling due to some lung pathology
- **CA- lung**→ There is no Hx of blood in sputum that is associated with weight loss, decrease appetite, change in the quality of voice (hoarseness), difficulty in swallowing and lumps

Scanned with CamScanner

and bumps in the body

- **Lung Abscess** →There is no HX of any chronic immunocompromised condition e.g. *IV* drug abuse DM etc. that is associated with high grade fever associated with chills and chest pain
- **sarcoidosis**→ There is no HX of painful lesions on shin that is associated with dry cough
- ***CCF/CHF/Cardiac Asthma*** →There is NO Hx of SOB that is associated with pink frothy sputum, distended neck veins and gen body swelling .or
- There is no Hx of SOB associated with disturbed night sleep that is relived with prop-up position
- ***Rheumatic heart disease***→ There is no HX of monthly intramuscular injection , abnormal movement of any part of the body
- **Ischemic heart Disease** →There is no Hx of SOB associated with left sided chest pain on exertion on background of smoking ,DM ,HTN, lipids disorders , sedentary lifestyle
- **Infective endocarditis**→ There is no HX of IV drug abuse ,recent instrumentation of the body &surgery ,tooth extraction ,high risk sexual behaviour
- **Connective tissue disorders and vasculitis**→ there is no Hx of oral ulceration, photosensitivity, hair fall, joint pain, skin rash, skin tightening and blood in sputum or urine → **Connective tissue disorders and vasculitis.)**
- **Anemia** →There is no Hx of SOB associated with Change in the complexion, palmar and conjunctival pallor, racing of heart beats and easy fatigability
- **CKD**→ There is no history of SOB associated with decrease urine output, blood or frothy urine and gen body swelling
- **CLD** →There is no Hx of blood in the vomitus, black tarry fouls smelling stools and abdominal distension
- **Hyperthyroidism**→ There is no Hx of associated with heat intolerance, excessive sweating, and involuntary movements of hands, loose motions and irritability ± swelling in the neck
- **Hypothyroidism**→ There is no Hx of cold intolerance, weight gain ,periorbital puffiness, sluggish mental activities , dry rough skin and hair ± swelling in the neck
- ***Neuromuscular disorder***→ There is no Hx of fluctuating weakness that is more at the end of the day associated with double vision or regurgitation of foods and difficulty in swallowing
- **Thromboembolism** →There is no Hx of prolong embolization , recent travel or surgery , family Hx of lower limb swelling

Exclude only few important relevant DDs in long case to save time otherwise you may not

Scanned with CamScanner

be able to complete the long case within 25 minutes.

Now apply CARE/RECA of your case

(COPD here)

CARE (Also Called RECA) stand for Aetiology, Risk Factors, Complication and Association

Aetiology and Risk Factors

As I mentioned earlier my patient has history of smoking of 30 pack years. He is very well aware of the adverse effects of smoking but he has never attempted to quit smoking .However, there is no history of exposure to biomass ,fuel, farm, factory, mines, animals pets birds, fumes dust and gas particles .My patient denied HX of yellow discoloration of sclera and lung disease in the family members (Alpha 1 antitrypsin deficiency). (So in the patient COPD is mainly due to smoking) .Now ask about the major complication of your long case, HX

Complications of COPD

1. **Right heart failure / Cor Pulmonale** there is HX (or no Hx as per your case findings) of distended neck veins, abdominal and lower limb swelling and yellow discoloration of sclera (Congestive Hepatopathy).
2. ***CO2 retention/narcosis*** there is Hx of early morning headache , altered sensorium and feeling of excessive warmness in the body
3. **Secondary Polycythaemia** There is no HX of redness of the skin, whistling sounds in the ear and itching after hot bath.
4. ***Respiratory failure and Cyanosis*** Hx of bluish discoloration of mucous membrane/ body and invasive/ non-invasive ventilation during hospital admission
5. **Lung CA** Hx of decrease appetite, change in the quality of voice (hoarseness), difficulty in swallowing and lumps and bumps in the body, muscle weakness and bone pain, constipation and dry mouth.
6. **Pneumothorax** HX sudden severe chest pain and shortness of breath that was relived with chest drain
7. **Repeated chest infection** HX of purulent sputum with fluid collection in chest cavity
8. **Medication like Steroid side effects** HX weight gain excessive hair growth acne newly diagnosed DM, HTN, and hoarseness' of voice e.g. iatrogenic cushingiods.

Now inquire about ITP i.e. relevant investigations treatment and any procedure (spirometery and bronchoscopy etc) done during the current admission.

Now Ask About RELEVANT

PAM HUGS FOSS TV F.

P →PAST HX

"HX dates back when my patient presented with SOB and went to a particular hospital or doctor etc. and describe briefly how and who diagnosed the disease e.g. what specific investigations were done like pulmonary function tests including spirometery and what was the result of those tests. Ask about at least 2-3 most recent hospital admission .Describe each in detail including investigation treatment including invasive and non-invasive interventions. Any other significant pre-morbid condition and inquire about it according to your time management.

Remember relevant past history is the part of the history of present illness.

Scanned with CamScanner

- **P** →personal HX ;like weight appetite sleep and bowel and bladder
- **A**→ Allergies HX ;ask about any allergies'
- **M**→ Medications HX ;Ask about medication frequency and dosage and its adverse effects
- **H**→ Hospitalization HX; ask how many times, reason and management including any complications.
- **U &G**→ (URO-GYNE HX)
- **S**→ Surgical HX; Bullectomy and lung volume reduction surgery etc
- **F**→ Family HX; ask about family HX of COPD (alpha 1 antitrypsin deficiency)
- **O** →Occupation (occupational exposure to coal dust ,silica ,cadmium)
- **S** → Sexual HX
- **S** → Socioeconomic HX (ask relevant socioeconomic Hx like factors that may prone him to COPD (or its exacerbation) and ask who take care of him including physical and financial support).
- **T** →Travel/Transfusion HX
- **V**→ Vaccination HX (Covid-19 , H influenza and pneumococcal)
- **F** →Functional status (include physical and mental impact of the disease).

Examination of COPD

- Start your examination after 8-10 minutes and take remaining history simultaneously.
    1. **Vitals**: First of all, measure BP at the right arm and put the thermometer in left axilla to record temperature.
    2. **GPE:** look for ;

Nicotine stain, flapping tremors, pepper thin skin , bruises , wasting of small muscle of the hands, palmar erythema, bounding pulse ,evidence of proximal myopathy, lymph nodes, JVP normal or raised , oral thrush ,anemia and jaundice, thyroid and pedal edema.

3. **Systemic Examination**

Request the patient to sit and expose him adequately. Now examine the back thoroughly according to the standard practice then examine front of the chest along with trachea, tracheal tug and measure cricosternal distance.

Next do CVS examination particularly look for signs of pulmonary hypertensions and right heart failure including comment on JVP.

During abdominal examinations, look for ascites, hepatosplenomegaly and purpura.

In neurological examination look for drowsiness confusion and syncope (type II resp failure) and do quick examination of motor and sensory system of upper and lower limbs including cranial nerves and Gait.

At the end of the examinations ask permission to check orthostatic hypotension (because CA LUNG may metastasis to adrenals) and do fundoscopy for papilledema that may be due to either metastasis or CO_2 narcosis.

Scanned with CamScanner

Presentation of the examination

On examination

- An old man who is thin, lean and emaciated sitting on a couch and remained co-operative throughout examination. He was in obvious respiratory distress.
- There was nicotine staining of 2nd and 3rd finger of the right hand. There was flapping tremor, bounding pulse that was in the range of 80-90 beats/minute and regular his BP was---- and temperature recorded--- C. Hands were warm. However, there was no clubbing, palmar erythema and cyanosis.
- There was redness of complexion, oral candidiasis and poor oral hygiene.
- JVP is normal/ raised and there was no lymphadenopathy.
- On examination of the back: His Chest was barrel in shape and moving more in the vertical plane with predominantly abdomino-thoracic pattern of respiration having a respiratory rate of 25 breaths per minute. He was using accessory muscle of respiration with intercostal, supraclavicluar and infraclavicluar recession. There was suprasternal and supraclavicular space excavation and there was pursing of lips. However, there was no gross chest deformity, prominent veins, scar marks and visible pulsation.
- Trachea was central with positive tracheal tug and cricosternal distance was decreased (less than 3-fingers). Apex beat was not palpable .Chest movements were bilaterally reduced and chest expansion was less than 3 cm. Vocal fremitus was reduced on both side.
- Percussion note was hyper resonant in both lung fields and there was loss of cardiac and liver dullness.
- The intensity of breath sounds was decreased with normal vesicular breathing with prolongs expiration. Expiratory rhonchi were scattered throughout the chest, and vocal resonance is also reduced
- Additionally, there was a left parasternal heave, and the first and second heart sounds were audible. The pulmonic component of the second heart sound was louder in pulmonic area (mention murmur if present).
- The liver was palpable, but the liver span was normal, and there was no evidence of free fluid in the abdominal cavity. There was/ no sacral or pedal edema.
- Motor, sensory systems and cranial nerves were unremarkable.
- GAIT examination was remarkable for proximal myopathy (Gover sign was positive).
- Fundoscopy was unremarkable.

So based on my history and examination, my clinical diagnosis (or differential diagnosis) is

1. COPD (more specifically emphysema or chronic bronchitis)
2. Chronic persistent asthma
3. Bronchiolitis obliterans (but there will be no HX of smoking and inspiratory ronchi on chest examination)

You must defend your first diagnosis, 2nd and 3rd differential diagnosis.

Scanned with CamScanner

What is COPD?

GOLD 2023 Definition of COPD

"COPD is a heterogeneous lung condition characterized by chronic respiratory symptoms (dyspnoea, sputum production, exacerbations) due to abnormalities of the airways (bronchitis and bronchiolitis) and /or alveoli (emphysema) that causes persistent, often progressive, air flow obstruction."

How would you investigate this patient?

- CBC → raised TLC , anemia & secondary polycythaemia
- ESR and CRP marker of infection
- S/E esp potassium
- ECG for RVH , MAT and AF
- X-ray chest PA view

No reliable radiographic signs that correlate with the severity of air flow limitation, however, it is essential to exclude alternative diagnosis like cardiac failure, lung cancer. Following feature may be visible on CXR in COPD patient.

  - Hyper inflated lung field
  - Low flat diaphragm
  - Hyper lucent lung fields
  - Long tubular heart shadow
  - Bullae

- ABGs for respiratory failure(inability to keep oxygen and/or CO2 levels within normal limit is respiratory failure)
  - Type 2 failure in chronic bronchitis
  - Type 1 in emphysema
- ECG RVH and pulmonary HTN
- 2D ECHO for cor Pulmonale
- Sputum for microscopy and culture & sensitivity.

Specific Tests

- **Pulmonary function test** including objective evidence of airflow obstruction by spirometery (PONK VALA TEST HWA THA?) Post bronchodilator FEV1/FVC < 70 % is diagnostic. Other findings include increased total lung capacity, increased functional residual capacity and residual volume. Decreased vital capacity and TLCO (CO transfer factor).
- If young patient with predominantly basal emphysema than alpha one anti-trypsin level.
- **Helium dilution technique** for measurement of lung volumes that in turn provide an assessment for hyperinflation, however in patients with severe COPD and those having large bullae then body plethysmography is preferred.

Scanned with CamScanner

- **HRCT** for characterization and quantification of emphysema and bullae

What Are the Risk of COPD?

Environmental factors	*Host Factors*
• Indoor air pollution in developing world • Occupational exposure to silica, coal dust and cadmium • Low birth weight , may reduce maximally attained lung function in young adult life • Recurrent infection , accelerate decline in FEV1 • Low socioeconomic status • Cannabis smoking	• Genetic factors alpha one anti-trypsin deficiency • Airway hyper- reactivity.

How will you assess severity of COPD?

Traditionally severity has been defined based on EFV % predicted. However, clinically relevant assessment of severity is based on impact of COPD on patients in terms of symptoms and limitation in activity and frequent and significant exacerbations.

Spirometric classification of COPD severity based on post –bronchodilator FEV1

Global initiative for obstructive lung disease (GOLD)

Severity of airflow obstruction Post –bronchodilator FEV1/FVC <0.7

FEV_1/FVC	FEV_1% Predicted		NICE Clinical guidelines 101 (2010)
<0.7	≥80%	Stage- I Mild	Stage I- mild
<0.7	50-79%	Stage-II moderate	Stage II- moderate
<0.7	30-49%	Stage-III severe	Stage III- severe
<0.7	<30%	Stage-IV very severe	Stage IV- very severe

How would you manage this patient?

1. Smoking cessation

What are the pharmacotherapies and pharmacological products for smoking cessation?

- Nicotine replacement therapy (NRT) like nicotine gums, inhaler, nasal spray, transdermal patch, sublingual tablets.
- Contraindications of NRT include recent MI or stroke. Start two weeks after the event.
- Bupropion, nortryiptyline and clonidine but the last drug is limited by its adverse effects.
- **How to calculate packs years** = (no of cigarette /20) × no of years

Scanned with CamScanner

2. Drugs according to the severity

- According to GOLD 2023 ABE TOOL (old was ABCD TOOL).
- A patient may fall into one of 3 categories. I.e. A B E based on assessment of symptoms /risk of exacerbation, mMRC and CAT score and would be treated accordingly.

MMRC Dyspnoea Scale

Grade	Degree of breathlessness related to activities
0	No breathlessness, except with strenuous exercise
1	Breathlessness when hurrying on the level or walking up a slight hill
2	Walks slower than contemporaries on level ground because of breathlessness or has to stop for breath when walking at own pace
3	Stops for breath after walking about 100 m or after a few minutes on level ground
4	Too breathless to leave the house, or breathless when dressing or undressing

What is CAT?

COPD assessment test called CAT is an 8-item questionnaire that assesses health status in COPD patient. The score range from 0 to 40.

- ❖ Do not memorized CAT score but only MMRC dyspnoea scale

Category A

Patients having mMRC 0-1 and CAT <10.

Category B

MMRC $\geq$ *2 and CAT* $\geq$ *10.*

While both categories may have 0 or 1 moderate exacerbation not leading to hospitalization

Category E

≥2 moderate exacerbation ≥1 leading to hospitalization.

Initial Pharmacological Treatment Based On ABE Tool

Group A

A bronchodilator (SABA (Salbo) or SAMA (tiovair))

Group B

LABA+LAMA*

Group E

LABA+LAMA* (TIOVAIR F)

Consider LABA+LAMA+ICS* if blood eosinophil's is 300 or more.

If patients treated with LABA+LAMA+ICS still have exacerbation then add Roflumilast.

- Roflumilast (PDE-4 inhibitor) has been shown to reduced exacerbation frequency in patients who have moderate or severe (FEV1 <50% of predicted) COPD and chronic

Scanned with CamScanner

bronchitis with frequent exacerbation and who are taking LABA/inhale corticosteroids with or without a LAMA.

- Add a macrolide azithromycin particularly in those who are ex-smokers.

Vaccination in COPD

- Influenza
- Covid-19
- One dose of PCV20 or PCV 15 followed by 23- valent pneumococcal polysaccharide vaccine(PPSV23) as per CDC recommend Tdap vaccination against pertussis(whooping cough) for COPDier that were not vaccinated in adolescent and zoster vaccine for those who are above 50 years .

What are the therapeutic interventions that reduce mortality in COPD?

- **Pharmacological therapy**
  - According to IMPACT and ETHOS clinical trials fixed –dose inhaled triple combinations (LABA+LAMA+ICS) reduce all –cause mortality compare to dual long-acting bronchodilation therapy.
- **Non –pharmacological therapy**
  - Smoking cessation
  - Pulmonary rehabilitation(PR)
  - Long term oxygen therapy(LTOT)
  - Non-invasive positive pressure ventilation(NPPV)
  - Lung transplantation and lung volume reduction surgery (LVRS).

What is pulmonary rehabilitation (PR)? Moreover, what are its advantages?

It is defined as , a comprehensive intervention based on thorough patient assessment followed by patient-tailored therapies that include ,but not limited to, exercise training ,education, self-management intervention aiming at behaviour change, designed to improve the physical and psychological condition of people with chronic respiratory disease and to prompt the long –term adherence to health –enhancing behaviours.

Advantages

- PR Improves dyspnoea, health status and exercise tolerance in stable patients.
- PR reduces hospitalization among patients who have had a recent exacerbation e.g. 4 or less than 4 weeks from prior hospitalization
- PR leads to a reduction in symptoms of anxiety and depression.

What do you know about Tele-rehabilitation?

It's new model of rehabilitation that is still evolving and best practices are not yet established.

What are the indications of LTOT?

1. $PaO_2 < 55$mm Hg(7.3kPa) or $SaO_2 < 88\%$ or
2. $PaO_2 > 55$ but <60 mmHg (>7.3 kPa but <8 kPa) with one of the following
   - right heart failure /Cor Pulmonale (peripheral edema)
   - Secondary polycythaemia

Scanned with CamScanner

- Nocturnal hypoxemia.

2-4 L /min oxygen at least 15hours/day to keep SaO $\geq$ 90 % o without unacceptable rise in $PaCO_2$

What are the benefits of LTOT?

- Improve secondary polycythaemia
- Decrease salt & water retention
- Decrease cardiac arrhythmias
- Decrease sympathetic outflow
- Improved quality of sleep at night due to reduced hypoxia induced sleep arousal.

How would you assess COPD patient for LTOT?

By measuring ABGs on two occasion at least 3 weeks apart in stable patient on optimum management and at least 4 weeks after exacerbation.

Active smoking is contraindication to LTOT.

Management of Exacerbations

Exacerbation is defined as an event characterized by dyspnoea and /or cough and sputum that worsen over <14 days which may be accompanied by tachypnea and /or tachycardia and is often associated with increased local and systemic inflammation caused by infection, pollution or other insult to the air-way.

DDs of acute exacerbation of COPD

- Pneumonia
- Heart failure, myocardial infarction and cardiac arrhythmias
- Pneumothorax and pleural effusion
- Pulmonary embolism.

How would you manage an exacerbation of COPD?

Summary for management of acute exacerbation as per GOLD 2023 guidelines

- Administer control oxygen therapy when required.
- Short acting inhaled beta2-agonists, with or without short-acting anticholinergic, is recommended as the initial bronchodilators to treat an exacerbation.
- Maintenance therapy with long-acting bronchodilators should be initiated as soon as possible.
- Inhaled corticosteroid should be added to those patient having frequent exacerbation or raised peripheral eosinophil levels
- In severe exacerbation, systemic corticosteroids can improve lung function (FEV1), oxygenation and shorten recovery time including hospital stay.
  - Duration of therapy should last no longer than 5days.
- Antibiotic, when indicated, can shorten recovery time, reduce risk of early relapse, treatment failure and hospitals stay.
- Non-invasive mechanical ventilation should be first mode of ventilation used in COPD patients with acute respiratory failure who have no absolute contraindication because it improves gas exchange, reduce work of breathing and need for intubation, decreases hospital

Scanned with CamScanner

stay and improve survival.

- Exacerbation recovery times vary among patient taking 4-6 weeks.
- monitors fluid balance
- Consider subcutaneous low molecular heparin for thromboembolism prophylaxis
- Identify and treat associated conditions like heat failure ,arrhythmias etc
- Determine the aetiology for exacerbation e.g. sputum culture, viral testing, CXR and others.

Pathogen causing exacerbations

1. Haemophilus influenzae (most common
2. Streptococcus pneumonaie
3. Moraxella catarrhalis
4. Respiratory viruses like human rhinovirus being the most important one.

What is the prognosis of COPD?

Prognosis of COPD is predicted by BODE index:

Variables	points on BODE index			
	0	1	2	3
FEV_1	≥65	50-64	36-69	≤35
Distance walked In 6 mins(m)	≥350	250-349	160-249	≤149
MRC Dyspnea scale	0-1	2	3	4
Body mass index	>21	≤21		
A patient with a BODE score of 0-2 has a mortality rate of around 10% at 52 months, whereas a patient with a BODE score of 7-10 has a mortality rate of 80% at 52 months				

What are the poor prognostic factors of COPD?

- Advancing age and fall in FEV1 (most important one)
- Weight loss
- Pulmonary hypertension

How would you classify the severity of COPD exacerbations?

It is classify into 3 types

MILD

- Dyspnoea VAS* < 5
- RR<24 breaths/min
- HR<95 bpm

Scanned with CamScanner

- Resting SaO2 92% ambient air
- CRP < 10mg/L

MODERATE 3 out of 5 points

- Dyspnoea VAS ≥5
- RR >24 breaths/min
- HR >95 bpm
- Resting SaO2 < 92% ambient air
- CRP ≥10mg/L
- ABGs may show hypoxemia (PaO2 ≤ 60 mmHg) and /or hypercapnia (PaCO2 > 45mmHg) but not acidosis.

Severe

Moderate COPD but ABGS shows hypercapnia and acidosis (PaCO2> 45mmHg and PH <7.35) is severe exacerbation of COPD.

- VAS* Visual analog dyspnoea scale.

What are the indications for Hospitalization?

- Severe symptoms such as sudden worsening of resting dyspnea, high respiratory rate, decreased oxygen saturation, confusion, drowsiness.
- Acute respiratory failure
- Onset of new physical signs e.g. cyanosis, peripheral edema
- Failure of an exacerbation to respond to initial medical management
- Presence of serious comorbidities eg heart failure etc.
- Insufficient home support.

What are the indications For Intensive Care Unit?

- Severe dyspnoea that response inadequately to initial emergency therapy ,
- Change in the mental status
- Persistent or worsening hypoxemia (PaO2 <5.3kpa or 40mmHg) and /or severe /worsening respiratory acidosis(PH <7.25) despite supplemental oxygen and non-invasive ventilation
- Needs for invasive mechanical ventilation
- Hemodynamic instability –needs for vasopressor

What are the indications for Non-invasive Mechanical Ventilation (NIV?)

- Respiratory acidosis (PaCo2 ≥ 6.0kPa or 45 mmHg and arterial P H ≤ 7.35)
- Persistent hypoxemia despite supplemental oxygen therapy.
- Severe shortness of breath with clinical signs of respiratory distress like using accessory muscle of respiration, paradoxical motion of the abdomen etc
- Type 2 respiratory failure secondary to chest wall deformity, neuromuscular disorders and obstructive sleep apnoea.
- Cardiogenic pulmonary edema unresponsive to CPAP.

Scanned with CamScanner

What are the indications of Invasive Mechanical Ventilation?

- When patient cannot tolerate or failure of NIV
- Life-threatening hypoxemia in patients unable to tolerate NIV.
- Massive aspiration or persistent vomiting
- Severe hemodynamic instability without response to fluid and vasoactive drugs
- Diminished consciousness, psychomotor agitation inadequately controlled by sedation.
- Severe ventricular or supraventricular arrhythmias.

What is the criteria for discharge and recommendation for follow- up?

Discharge criteria

- Full review of all clinical and laboratory data.
- Check maintenance therapy and patient understanding
- Reassess the inhaler technique
- Ensure understanding of withdrawal of acute medications (steroids and/or antibiotics)
- Provide management plan for comorbidities.
- Ensure follow-up managements
    - Early follow-up <4 weeks and late follow-up 12 weeks as indicated while during each visit evaluate the patient thoroughly and address the concerns.

COVID-19 and COPD

Mild COVID-19

- Continue COPD Therapy

Moderate COVID-19

- Systemic steroid, anticoagulation, remdesivir and IL-6 tocilizumab

Severe COVID-19/ARDS

- High flow oxygen, pruning, anticoagulation, NIV or Mechanical Ventilation

Interventional & surgical therapies for COPD

1. Bullectomy
2. Endoscopic lung volume reduction surgery this may be unilateral or bilateral.
3. Endo bronchial one-way valves
4. Airways bypass stents.
5. Self-activating coils

Above all measures are mainly directed to reduce hyperinflation in emphysema.

Indication for lung transplant

- When Bullectomy and other intervention are not possible
- Pulmonary hypertension
- BODE index 7-10.

Scanned with CamScanner

Differences between Chronic Bronchitis and Emphysema

Features	Emphysema: (Pink Puffer)	ChronicBronchitis:(Blue Bloater)
Diagnosis	Clinical	Pathological
Cyanosis	Absent	Prominent
Hyperinflation features	++	+
Dyspnoea	++	+
Cough	+	++
Cor pulmonale	+	++
Thin /obese	Thin	Obese
Pulmonary function test	TLC raised and DL co reduced. Static lung compliance increased	TLC normal and DLco normal. Static lung compliance normal
Ventilation-perfusion Testing	Increased ventilation to high V/Q areas i.e. high dead space ventilation.	increased perfusion to low V/Q areas

Bullets points of COPD

Essential of diagnosis of COPD

- COPD is a major cause of chronic morbidity and is the third leading cause of death worldwide.
- One study of active smokers reported yearly decreases in FEV1 of 66mL per year in men and 54 mL per year in women compared to 30ml per year in men and 22mL per year in women who sustained smoking cessation. Therefore, smoking cessation is the single most important intervention.
- A 6 –minute walking distance of less than 350m is associated with increased mortality..
- Tran's nasal positive-pressure ventilation at home to rest the respiratory muscles is an approach to reduce dyspnoea in-patient with severe COPD.
- Increased exacerbations and mortality reported in some asthmatic patient treated with salmeterol have not been observed in COPD.
- CMDT 2023 labeled theophylline as fourth-line agent for treating COPD. Apart from bronchodilation, it has anti-inflammatory properties, strengthen diaphragm, and improve myocardial contractility and kidney function. However, it has narrow therapeutic window.
- Expectorant –mucolytic therapy is not helpful in chronic bronchitis.
- Apart from acute exacerbations, COPD is not generally responsive to oral steroid therapy.
- Supplemental oxygen for patients with resting hypoxemia (PaO_2 <56 mmHg) is the only therapy with evidence of improvement in the natural history of COPD.
- Target O2 sat% in COPD patient and principal of O2 therapy in respiratory failure.
    - COPD patient with high PCO_2 target O2 is 88-92%
    - COPD patient with normal PCO_2 target O2 is 94-98%.

Scanned with CamScanner

- type1 –high concentration (i.e. .>35% usually 60%) /high flow (6-8L/min)
- Typ2 –low concentration (24-28) /low flow (1-2L/min).

What are the Recent Advances in COPD?

Long acting anti-muscarinic drugs (LAMA) like Revefenacin, Umeclidinium, and Aclidinium bromide.

Scanned with CamScanner

APPROACH TO SOB (Due to Asthma)

P/C

- worsening of shortness of breath 6 days
- cough (for approach to cough see next section)

HOPI (*ODPARA*)

My patient who is non-smoker, normotensive and normoglycemic has been suffering from episodic shortness of breath for the last 3 years that occur more frequently during the spring, summer season and rainy weather and remain completely asymptomatic between the attacks but since last -6 days, he has persistent shortness of breath.

Shortness of breath was gradual in onset and progressive in nature as initially he was able to do his routine activities but for the last 3-days due to shortness of breath he cannot cope with his daily activities and it is aggravated by dust and now partially relived by inhaler which he has been using with proper technique and has good compliance. He used inhaler when required but for the last-6 days he uses inhaler multiple time during day and nights with minimal reliefs .Shortness of breath associated with whistling sound in breathing and chest tightness .it is also associated with cough that is gradual in onset and worse at night and early morning .cough is predominately dry; however with occasional sputum production that is 1-2 tea spoon in quantity, non-foul smelling, whitish in color and having no-blood. It is aggravated by exposure to dust and now partially relived by inhaler and cough syrup. It is associated with disturbed night sleeps since last-3 days. However, my patient denied any history of.....

Now exclude important DD, s of shortness of breath in HOPI as discussed in COPD.

Most importantly exclude cardiac asthma, COPD, churg-strauss syndrome, eosinophilic pneumonia, hypersensitivity pneumonia, bronchiectasis, vocal cord dysfunction and conversion disorder like functional asthma.

- ***CCF//Cardiac Asthma*** →There is no HX of distended neck vein , lower limb swelling , SOB on exertion and lying flat , associated with disturbed night sleep that is relived with prop-up position
- ***Bronchiectasis***→ There is no HX of copious amount of foul smelling sputum that is worse in the morning and expectorates at certain position
- **COPD** → there is no HX of active or passive smoking /biomass, fume, factory and dust exposure associated with SOB& wheezy chest that is worse during winter and rainy season
- **Churg-strauss syndrome**→ there is no HX of decreased urine out-put ,tingling or numbness of hand feet and nasal polyps associated with SOB & wheezy chest sounds
- and so on as discussed in COPD section

CARE/ERCA

Etiology and risk factors

- there is no Hx (or Hx as per your actual case) of allergy (or exposure) to pollen, home dust, fumes &fog, smoke, animal dander.(Allergic asthma
- There is no HX of skin allergies, allergic rhinitis, **(Allergic Asthma**

Scanned with CamScanner

- There is no HX of excessive weight gain(**obesity induced asthma**)
- There is no HX of occupational exposure to dust, fume, isocyanataes cobalt(**occupational asthma,**
- There is no HX of shortness of breath during or after exercise (**exercise induced asthma**
- Catemenial asthma (**asthma attack during menstrual cycle**)
- There is no HX of intake of aspirin, NSAID, B blocker (**drug induced asthma**
- There is no HX of retrosternal and epigastric burning(**GERD Induced Asthma**
- There is no HX of recent flu, fever, purulent sputum and cough and postnasal drip (**Infective Exacerbation of Asthma.**
- There is no HX of peripheral eosinophilia and evidence of proximal bronchiectasis on labs associated with these symptoms **(ABPA).**

Complications of asthma

- Hx of bluish discoloration of skin /mucous membrane, drowsiness and admission into intensive care unit (**severe exacerbation of asthma**
- Hx of admission into high dependency unit and mechanical ventilation (**life threatening exacerbation**
- HX sudden severe chest pain and shortness of breath that was relived with needle aspiration or chest drain(**pneumothorax**)
- HX weight gain excessive hair growth, acne newly diagnosed DM& HTN and hoarseness of voice (**Iatrogenic cushingiods**).
- Hx of palpitation, tremors and dry mouth (**medication side effects**)

Association

- Churg-strauss syndrome (CSS)→ Hx of asthma associated with any neurological deficit like hand or foot drop, haemoptysis, haematuria and peripheral blood eosinophilia >10%.
- Allergic Broncho pulmonary Aspergillosis(ABPA
- There is no HX of peripheral eosinophilia and evidence of proximal bronchiectasis on labs associated with these symptoms (**ABPA**).
- Carcinoid syndrome(least association)
    - Hx of wheezing and shortness of breath and loose motion
- Now ask for **ITP** i.e. investigations, treatment and any procedure like spirometery **(PONK VALA TEST)** for current admission.

Past History

- Hx dates back 3years when my patient experienced shortness of breath & cough for which he booked an appointment with….etc. now ask detail how and who diagnosed him what investigations were carried out(esp. pulmonary function tests including spirometery)and what treatment was recommended ,compliance and inquired particularly about detail of previous exacerbations and its management and control of symptoms. Ask other

Scanned with CamScanner

significant premorbid according to your time management.

Now ask relevant

- PAM HUGS FOSS TV F.
- Ask family HX of atopy and asthma.

Examination scheme

Same as for COPD

GPE →Cushingoid appearance

CNS → neuropathy (churg-strauss)

Based on history and clinical examination my clinical diagnosis or differential diagnosis includes,

- Asthma.
- Allergic bronchopulmonary aspergillosis
- Obstructive pulmonary disease like COPD
- Churg-strauss syndrome

Always tell 2 or maximum 3 closed logical differentials and defend it.

Scanned with CamScanner

VIVA OF ASTHMA

- For COPD memorized latest GOLD guidelines while for asthma GINA* guidelines, for FCPS-II exam.

Define asthma according to GINA guidelines.

Asthma is a respiratory disorder characterized by symptoms such as wheezing , shortness of breath ,chest tightness and cough that vary over time in their occurrence ,frequency and intensity .these symptoms are associated with variable expiratory airflow i.e. difficulty breathing air out of the lung due to bronchoconstriction, airway wall thickening and increased mucus.

What are the different phenotypes /variants of asthma?

Asthma is broadly divided into allergic and non- allergic asthma.

- **Allergic,** the most common and may be associated with other allergic diseases like allergic rhinitis, eczema since childhood.
- **Asthma with obesity**
- **Occupational asthma,** patients are characteristically better when on holiday .isocyanates cobalt is the most common cause other agent may include platinum salt, epoxy resins and flour. May occours weeks to years after initial exposure and sensitization?
- **Exercise induced asthma, begins** during exercise or within 3 minutes after its end.
- **Cough variant asthma,** predominant symptoms is cough instead of wheezing.
- **Cardiac asthma,** wheezing and shortness of breath due to pulmonary congestion in the setting of decompensated heart failure.
- **Drug induced asthma, aspirin**, NSAID and tartrazine dyes and beta-blockers.
- **Asthma** induced by nonspecific precipitants like upper airway infection, postnasal drip , GERD, stress, change in weather and air pollution like ozone,SO_2 and NO_2
- **Upper air way obstruction and paradoxical vocal fold motion** ;can also present with shortness of breath and wheezing

- * **www.ginaasthma.org**

How will you investigate this patient?

- **CBC→** to look for eosinophilia.
- **Sputum; C/S & G/S→** for charcot-leyden crystals and Churchman's spirals (non-specific.
- **CXR PA view→** to look for complication like pneumothorax and exclude alternative diagnosis like COPD and cystic fibrosis etc.
- Pulmonary test including spirometery with reversibility; See below
- **Peak expiratory flow (PEF) meter →**to confirm the diagnosis of asthma, quantify its severity, and established peak flow variability. A 20% change in PEF values from morning to afternoon or day to day denotes inadequately controlled asthma while PEF < 200ml/min indicate sever airflow obstruction .predicated values of PEF depends on age , gender and height. It is the bedside test for asthma
- **IGE level→** (to look for ABPA and CSS).
- **pANCA →** (to exclude CSS where it is positive in 60%)

Scanned with CamScanner

- **skin allergic tests** →(prick and patch tests)
- **absolute eosinophil count** →for anti-interlukin-5 therapy
- **ABGs**→ may be normal in **or** there may be respiratory alkalosis in mild exacerbation.

Criteria for asthma diagnosis

Asthma has two key defining features

1. **A history of variable respiratory symptoms**

Typical symptoms are wheeze, shortness of breath, chest tightness, and cough;

- People with asthma have one or more symptoms
- The symptoms are variable over time and vary in intensity
- The symptoms often occur or are worse at night or early morning.
- Symptoms are often triggers by exercise ,allergens or cold air
- Symptoms often occur with or worsen with viral infections.

2. **Evidence of variable expiratory airflow limitation**

Clinical diagnosis of asthma is made when compatible history plus either

- FEV1 ≥ 12 %(and 200ml) increases following administration of a bronchodilators /trial of glucocorticoids or
    - Greater confidence is gained if the increase is > 15% and >400ml
- >20% diurnal variation on ≥ 3days in a week for 2 weeks on PEF dairy or
- FEV1 ≥ 15% decrease after 6 mins of exercise.

- Once asthma has been diagnosed, the lung function is the most useful as an indicator of future risk. It should be recorded at the diagnosis, 3-6 months and then periodically.
- Testing may needs to be repeated during symptoms, in the early morning, or after withholding bronchodilator medications.
- Significant bronchodilators reversibility may be absent during sever exacerbations or viral infections.

Confirmation of Diagnosis of Asthma in Patient Taking Controller Treatment

If the standard criteria are not met like pulmonary function is normal, then repeat reversibility testing when patient is symptomatic , or after holding SABA for> 4 hours, twice-daily ICS-LABAs for >24 hours, and once-daily ICS-LABAs for >36 hours

How would you assess a patient with asthma?

By following tools

1. **Asthma control ----- assess both symptom control and risk factors**

   Asthma control means the extent to which the effect of asthma can be seen in the patient, or have been reduced or removed by treatment.

A. Assessment of asthma Control

- Day time symptoms more than twice a week
- Night time awakening due to asthma
- Reliever medication needed more than twice a week
- Any activity limitation due to asthma

Scanned with CamScanner

Well Controlled

- if none of these components within past 4 weeks

Partly Controlled

- If 1 or 2 of these components within past 4 weeks

Non Controlled

- if 3-4 of these components within past 4 weeks

B. Risk factors for poor asthma outcomes

- **medications;** ICS not prescribed ; poor compliance , incorrect techniques , high SABA use(associated with increased exacerbation if ≥3 into 200-dose- canister /year and increased mortality if ≥ canister per month)
- **Comorbidities;** obesity, chronic rhino sinusitis, GERD, confirmed food allergy, depression and pregnancy.
- **Exposure;** smoking, allergens exposure if sensitized including occupational, air pollution.
- **Setting;** major socioeconomic problems.
- **Lung function** ; low FEV1, especially if < 60% predicted
- **Intensive –care admission or** ever being intubation and > 1 exacerbation in the last 12-months.

Having any of these risk factors increases the patient's risk of exacerbations even if they have few asthma symptoms.

II. **Are there any comorbidities** → these include obesity, chronic rhino sinusitis, GERD, depression & anxiety and obstructive sleep apnea. Comorbidities should be identified as they may contribute to flare-up and poor quality of life. Their treatment may complicate asthma management.

III. **Treatment issues** →Inquire the patient about their goals and preferences for asthma treatment. Watch the patient using their inhaler, to check their techniques and ask about compliance and side effects of treatment.

How would you manage this patient?

There are 5 important aspect of chronic asthma management

Assessing Asthma Control and Severity

Assessing asthma control is discussed above while the asthma severity is evaluated retrospectively from the level of treatment needed to control symptoms and exacerbation. Typically, mild asthma responds to step i or ii treatments, moderate asthma to step 3 treatment and severe asthma to step 4 or 5 treatments.

Pharmacological Therapy for Asthma

Memories this entire step for FCPS viva

- GINA (2021) no longer recommends treatment of asthma with short-acting beta$_2$ agonists (SABA) alone.

There are 5 steps of pharmacological management of asthma as maintenance and reliever

Scanned with CamScanner

treatment (MART) for adult and adolescent (≥ 12years).

- **Step I & II**

As needed low dose ICS & formoterol
(200mcg budesonide &6mcg)

- **Step III**

Low dose maintenance ICS& formoterol
(200mcg &6mcg BD)

- **Step IV**

Medium dose maintenance ICS& formoterol
(400mcg &6mcg BD)

- **Step V**

Add-on LAMA +high dose ICS & formoterol and refer for phenotypic assessment
(400mcg & 6mcg TDS)

- **Step V phenotype assessment**

If patient is on step V and still symptomatic

a. **Anti IgE level:**
If raised then it is allergic asthma.

Rx treatment: Omalizumab + steroids+ ICON? (Kindly confirm this point by yourself as this point was taken during a lecture)

Omalizumab SC ≥ 6 years

b. **Eosinophilic asthma:**
If blood or sputum eosinophil count > or 300 then treat with
Anti-IL 5 (SC mepolizumab, ≥ 6 years or IV resilizumab, ≥ 18 years) or anti-IL5 or (SC benrilozumab, ≥ 12 years) or Anti-IL-4R (SC dupilumab, ≥ 12 years)

c. **Non eosinophilic Asthma**
In this phenotype of asthma, neither IgE nor eosinophil counts are raised. It is treated with

LAMA + LABA + theophylline + macrolides (azithromycin)

GINA classify non eosinophilic phenotype as severe asthma and recommends anti TSLP (thymic stromal lymphopoietin; an epithelial- cell derived cytokine implicated in the pathogenesis of asthma) Tezepelumab"

- ICS- formoterol is preferred reliever and controller. As a reliever, this reduces the exacerbation compared to using a SABA reliever.
- Low dose ICS Budesonide 200-400, medium dose > 400-800 and high dose is >800mcg.

How to start pharmacological treatment?

In adult and adolescent with a diagnosis of asthma;

- If symptoms less than 4-5 days a week, treat with step I-II (MILD ASTHMA
- Symptoms most days, or waking with asthma once a week or more, treat with step III (MODERATE ASTHMA.

Scanned with CamScanner

- Daily symptoms, or waking with asthma once a week or more and low lung function, treat with step IV (SEVERE ASTHMA); short course of Oral Corticosteroid may also be needed for patients with severely uncontrolled asthma.
  - **Uncontrolled vs. severe asthma**

If patient is, using step 4 or 5 treatment but still symptomatic it is prudent to distinguish between uncontrolled and severe asthma. Here clinicians must assess patient compliance, inhaler technique and comorbid like GERD, obstructive sleep apnea and on-going exposure to allergens as a cause of poor control of asthma that is termed as uncontrolled asthma. If the patient is, still require Step 4 or 5 treatments when the above etiology has been excluded or addressed, then the patient has severe asthma and should be referred to a pulmonologist.

- **Treat modifiable risk factors and control environmental factors.**

These factors have been discussed above in assessing asthma control section. Like reduction of exposure, to non- specific irritant in all asthmatic patients and, to inhaled allergens in atopic patients may reduce symptoms. Likewise, certain medical conditions that impair asthma management such as obesity, GERD, smoking, rhino sinusitis and smoking should be identified and treated.

Guided asthma self –management education and skills training.

Self –management includes monitoring of symptoms or peak flow, a written action plain, and regular review of asthma control, treatment and skills with a health care professional.

How often should patients with asthma be reviewed?

The frequency of review depends on the patient's initial level of symptom control, their rest factor and response to initial treatment. Patient should preferably be seen 1-3 months after starting treatment and every 3-12 months after that but in pregnancy, Asthma should be reviewed after every 4-6 weeks. After an exacerbation, a review visit within one week should be scheduled.

Immunotherapy and asthma (Desensitization therapy)

Allergen –specific immunotherapy (ASIT), involves the repeated administration of allergen products to induce immunological and clinical tolerance to that specific allergen.

Allergen immunotherapy is of benefit in highly selected patients with defined allergic triggers. Asthmatic patient with single specific allergic trigger and concomitant nasal symptoms derive the greatest benefit compared with patients with multiple allergic triggers.

There are two routes.

I. cutaneous immunotherapy (SCIT)

Allergen-specific immunotherapy (ASIT) may be given subcutaneously. There is a risk of adverse effects, including anaphylaxis.

II. sublingual immunotherapy (SLIT)

Sublingual ASIT has recently been shown to be an effective and safe alternative in patients with seasonal allergy.

MR X is cardiac patient and he has aspirin induced asthma too, how would you treat him?

Desensitization therapy for aspirin

When to step-up or step-down in asthma management?

Scanned with CamScanner

If symptoms not controlled step-up in 2-4 weeks
If symptoms controlled step-down in-6 months

Asthma flare-ups (Exacerbations)

Management of Asthma Exacerbation

Asthma flare-ups or exacerbation is an acute or sub-acute worsening in symptoms and lung function from patient's usual status; occasionally it may be the initial presentation of asthma.

Management of Asthma exacerbation in primary care

See CMDT table

Management of Asthma exacerbation in acute care facility

See CMDT table

DD's of exacerbation (rule out)

- Heart failure
- Pulmonary embolism
- Inhaled foreign body
- Upper airway dysfunction.

Asthma-COPD overlap syndrome (ACOS).

Asthma and COPD may co-exist or overlap called asthma –COPD overlap syndrome (ACOS). It is more common in smokers and the elderly. Asthma-COPD has worse outcomes than asthma or COPD alone, therefore, whenever there is uncertainty about the diagnosis early referral should be made. Treatment is ICS+LABA or ICS+LABA+LAMA.

All 3 major and 1 minor criteria is require for diagnosis

Major

- Very positive bronchodilator test
  (Increase in FEV1 $\geq$ 15% and $\geq$ 400 ml over baseline)
- Eosinophilia in sputum
- Personal history of asthma (before the age of 40).
- 10 pack smoking HX or air pollution HX.

Minor

- High total IgE
- Personal history of atopy(eosinophil > 300
- Positive bronchodilator test

(Increase in FEV1 $\geq$ 12% and $\geq$ 200ml) on two or more occasion

Marker of COPD is YKL-40 and of asthma is periostin while in overlap syndrome both markers are positive.

Types of Inhaler

- **Meter Dose inhaler (MDI),** like Salbo, Foster with or without spacer.
- **Dry powder inhaler (DPI),** like Rota inhaler (Combivair)
- **Soft Mist Inhaler,** most efficient but it is not available in Pakistan
- **Nebulizer,** high dose drug has to be given (during an exacerbation).

Scanned with CamScanner

Pregnancy and asthma

All asthmatic drugs are safe in pregnancy and breast-feeding.

COVID & asthma

Asthma does not increases risk of being infected with COVID-19, or of having severe COVID-19

Tell me most frequently reported causative agents in occupational asthma?

Isocyanates, flour and grain dust, latex, animals, aldehydes, and wood dust.

Tell me workers most commonly reported to occupational asthma canters

Paint sprayers, Nurses, Bakers, pastry-makers, and chemical workers.

PEARL OF ASTHMA

- Asthma is slightly more common in male children and in female adult.
- During severe exacerbation, airflow may be too limited to produce wheezing and only diagnostic clue may be globally reduced breath sounds on auscultation.
- Combination of an increased $Paco_2$ and respiratory acidosis may indicate impending respiratory failure and the need for mechanical ventilation.
- Bronchoprovocation is not recommended if the FEV1 is less than 65 % of the predicted.
- A positive methacholine test is defined as fall in FEV1 of ≥20% at exposure to a methacholine concentration of < **8mg** /ml. Negative test has a negative predictive value for asthma of 95%.
- SABA is the most effective bronchodilators during exacerbation and provides immediate(less than 5 minutes) relief of symptoms.
- Asthmatic patient who are treated with SABA alone are at increased risk of asthma-related death
- LABA should not be used as monotherapy because monotherapy is associated with small but significant increased risk of severe or fatal asthma attack.
- Minimally effective dose of systemic corticosteroid for asthma patient has not been established but for outpatient prednisone " burst" therapy is 0.5-1mg /kg /day in 1-2 doses for 3-7 days while for hospitalized patient prednisolone dose is 1mg/kg 6-12 hours for 48 hours or until
- Bone mineral density testing after 3 months or more of systemic corticosteroid exposure may guide for bisphosphonates treatment for steroid-induced osteoporosis.
- SAMA is the inhaled drug of choice for patients who are intolerant to SABA or with bronchospasm due to beta –blocker medications.
- Mast cell stabilizer like Cromolyn Sodium and nedocromil has good response in exercise-induced bronchospasm
- montelukast is effective for post-nasal drip
- Adult asthmatic- patients aged 19-64 should receive the pneumovax 23 and annual influenza vaccination.
- In severe exacerbation, early initiation of oxygen therapy is paramount because asphyxia is a common cause of asthma death.

Scanned with CamScanner

APPROACH TO ALLERGIC BRONCHOPULMONARY ASPERGILLOSIS

P/C: worsening of asthma

Aspergillus fumigatus is the usual cause of aspergillosis. The lungs, sinuses or the brain are the most involved organs .clinical illness result from immunologic response or tissue invasion .it is transmitted to humans via inhalation

There are 3 major clinical forms.

1. Chronic Aspergillosis (Aspergilloma)

It is a spectrum of disease that occurs on the background of pre-existing lung damage but patients are not in significant immunocompromised state. The spectrum range from aspergilloma (a fungal ball within a pre-existing lung cavity that may have resulted from TB, sarcoidosis or other necrotizing pulmonary pathology) to chronic fibrosing pulmonary aspergillosis. It is usually asymptomatic but may be characterized by long standing symptoms such as cough, shortness of breath, weight loss, malaise and haemoptysis. Chest x-ray may show a rounded opacity surrounded with a rim of air and there are serum high titres aspergillus precipitins antibodies in 95% cases of aspergilloma

The most effective treatment of symptomatic aspergilloma is surgical resection. Other forms of chronic aspergillosis are treated with azole therapy like itraconzoale 200mg BD, Voriconazole 200mg BD for 4-6 months.

2. Invasive Aspergillosis

Invasive aspergillosis develops mainly in immunocompromised individuals like hematopoietic stem- cell transplant, leukaemia, advanced AIDS and prolongs corticosteroid therapy. Pulmonary disease is the most common, with patchy infiltration leading to a severe necrotizing pneumonia. It typically manifests with fever, cough, and dyspnoea and pleuritic chest pain.

Definitive diagnosis is by microscopy and depends upon the demonstration of the organism in the tissue or culture from a sterile site (rarely done). Indirectly diagnostic assays include detection of galactomannan in bronchoalvelolar layage fluid or serum, or serum assays for 1- 3 beta –D-glucan (not specific for aspergillus). Imaging may also be helpful like CXR, HRCT chest where it may show, an air crescent sign.

Voriconazole (6mg /kg IV twice on day 1 and then 4mg/kg every 12 hourly or isavuconazole (200mg every 8 hourly for six doses, then 200mg daily) are first line therapy. others alternative options include liposomal amphotericin B (3-5mg/kg/day), caspofungin (70 mg on day 1 then 50 mg) and posaconazole oral tablet (300mg twice daily then 300 mg once daily).treatment duration depends on clinical response but 6-12 weeks is usual duration . surgical debridement is recommended particularly for sinusitis , focal pulmonary lesion especially life threatening haemoptysis and infection reluctant to medical therapy.

3. Allergic Bronchopulmonary Aspergillosis (ABPA)

- **Important for FCPS long-case**

Allergic bronchopulmonary aspergillosis is type iii hypersensitivity reaction to aspergillus fumigatus and commonly occurs in patients with pre-existing asthma or cystic fibrosis (CF), and

Scanned with CamScanner

bronchiectasis. In **cpsp exam,** the patient may have asthma (or less likely CF) that is worsening despite on maximum management. You have to exclude all major 3 forms by asking relevant questions like HX of asthma, bronchiectasis, past Hx of TB, immunocompromised conditions, chemo& radio exposure, long-term steroid therapy, and IV drug abuse.

What is the name of diagnostic criteria of ABPA or how would you diagnose ABPA?

The diagnosis of APBA is based on appropriate clinical feature in combination with supporting radiological (transient infiltrates and bronchiectasis) and serological findings. All asthmatic with difficult-to- control asthma are screened by checking for an elevated eosinophil counts, total IgE, and specific IgE A. fumigatus.

- **Rosenberg-Peterson criteria***

This include major and minor criteria

Major criteria (mnemonic ARTEPICS)

A Asthma
R Roentgenogaphic Fleeting Pulmonary Opacities
T Skin Test Positive for Aspergillus (Type 1 Reaction
E Eosinophilia
P Precipitating Antibodies (IgG) In Serum
I IgE (total) in Serum Elevated (>1,000 IU/Ml)
C Central Bronchiectasis
S Serum A fumigatus-specific IgG and IgE (more than twice the value of pooled serum samples from patients with asthma who have aspergillus hypersensitivity)

Minor Criteria

- Presence of aspergillus in sputum
- Expectoration of brownish black mucus plugs
- Delayed skin reaction to aspergillus antigen (type iii reaction)

*the presence of 6 of 8 major criteria makes the diagnosis almost certain;

APBA is further classified as ABPA-S or ABPA-CB on the absence or presence of central bronchiectasis, respectively.

What are the clinical stages of ABPA?

There are 5 stages of ABPA

I Acute. ii Remission. iii Exacerbation /Recurrence. iv Steroid-dependent asthma. V Fibrotic lung disease.

The detail description of each stage is beyond the scope of this book.

Treatment of ABPA

The goal of treatment of ABPA consists of controlling symptoms, preventing exacerbations and preserving normal lung function.

- Prednisolone 0.5-1mg /kg a day for 2 weeks, followed by 0.5mg /kg every other day for 6 to 8 weeks with a taper (by 5-10mg every 2 weeks) over weeks to months. This leads to relief of symptoms, decreased in airflow obstruction, greater than 35% reduction in serum IgE,

Scanned with CamScanner

reduction in peripheral blood eosinophil and resolution of pulmonary infiltrates.

- Itraconzoale 200mg orally twice daily for 16 weeks led to significant reduction in corticosteroid dose, appear to improve pulmonary function, decrease in IgE levels and pulmonary infiltrates.
- While Voriconazole is an alternative agent, others antifungal are generally ineffective and ketoconazole utility is limited by its hepatotoxicity.

Worsening asthma →do skin prick test for A.fumagitus if positive → do serum total IgE level, if it is more than 1,000 than it is ABPA and treat it. If in the range of 500-1000 monitor 6 monthly and if < 500 monitor annually. However, in cystic fibrosis patient if > 500 treatment is indicated

How to check response?

35-50% reduction in peripheral IgE level is good response to treatments. After 3- months of treatment (steroid) withdrawal if the patient is asymptomatic than it is in remission phase

What are the Recent Advances in treatment of ABPA?

Biological agents like OMALIZUMAB (in dose of 375mg SC every two weeks) may improve disease activity and spare oral corticosteroids. The more recently developed biological agents like dupilumab (directed against IL-4/13), mepolizumab (against IL-5) etc. are being used with some anecdotal successes in ABPA (ref; Fishman-6th edition

Scanned with CamScanner

APPROACH TO BLOOD IN THE SPUTUM (Due to CA Lung)

P/C

Blood in sputum 2 months

HOPI (ODPARA-V)

My patient who is chronic smoker with … Pack years presented with blood in sputum (do not use medical terminology during HX presentation) for the last…….. duration. It is episodic in nature, 8-10 episodes per day, and each episode containing 1-2 spoon of blood that is bright red and sometime are in clotted form however, there is no history of bleeding from any other body orifice and easy bruising.

Now apply ODPARAV

Associated features

- cough (dry or sputum production)
- SOB & wheezy chest sounds
- unintentional weight loss , decreased appetite and fever
- lumps& bumps
- Chest pain and palpitation.

Now exclude important DDS of lower groups

- **CA Lung (long case here)**
- **Pulmonary tuberculosis** →denied past or contact HX of TB or HX of low grade fever ,night sweats ,weight loss and lumps & bumps
- **Bronchiectasis** → No HX of passage copious amount of foul –smelling sputum particularly in the morning with postural drainage.
- **ABPA** →Denied Hx of chronic whistling sound in breathing, chronic use of inhaler or chronic Hx of SOB not responding to any medications.
- **(vasculitis like Wagner, microscopic polyngitis, good pasture etc**→ No Hx of palpable skin rash, blood in urine and arthritis or arthralgia
- **Autoimmune /SLE Induced (Alveolar Haemorrhage**→ no Hx of oral ulcer , photosensitivity, hair fall and arthralgia
- **lung abscess** →no Hx of IV drug abuse ,immunosuppressive medication ,aspiration of oral contents , poor oral hygiene and alcoholism
- **Coagulopathy** → denied family HX of any bleeding disorder or HX of blood thinning medication
- **Necrotizing Pneumonia**→ Denied Hx of high grade fever associated with rigors and chills
- **Pulmonary embolism** →no Hx of prolong immobilization ,recent air travel or surgery and unilateral swelling of lower limb
- **HIV**→ no Hx of high risk sexual behaviour ,unscreened blood transfusion and iv drug abuse
- **CKD**→ no HX of decreased urine output , periorbital swelling, sallow complexion of skin

Scanned with CamScanner

- **CLD→** No Hx of abdominal distension, blood in vomiting, tarry stool and past HX of HBV or HCV infection
- **(Valvular heart diseases e.g. Ortner syndrome)**

No Hx of left side chest pain, palpitation, monthly use of intramuscular injection difficulty in swallowing or change in the quality of voice

Most common causes of blood in sputum in exam are TB, CA lung, bronchiectasis, ABPA and vasculitis.

CARE/RECA of CA lung

Etiology /risk factor

- There is HX of smoking ….pack-years. Patient is well aware of the adverse effects of smoking but never attempted to quit .there is no Hx of other substance –abuse.
- There is no Hx of chronic alcohol intake or long standing lung diseases or prolong exposure to gaseous, fumes, particles and chemicals(like arsenic ,chromium, nickel, iron oxide) or farm, factory and mine work.
- Patient denied any family history of malignancy or use of drugs like chemotherapy or radiation therapy.
- patient denied any Hx of chronic SOB & cough associated with wheezy chest sound that is worse during winter →COPD)
- Shortness of breath on exertion associated with dry cough (ILD) and /or painful lesion on shin (sarcoidosis).

Complications/Association

(Remember mass effects, metastatic, treatment (chemotherapy or radiotherapy), Para neoplastic & hormonal association and complications)

- Patient denied any history of recurrent chest infections, fluid or puss collection in the lung.
- No Hx of difficulty in swallowing , hoarseness of voice, engorged veins in neck and a facial redness, (mass effect),
- No Hx of Drooping of one eyelid, loss of sweating in the half of face or wasting of small muscles of hand, numbness, tingling (Horner syndrome.
- no Hx facial puffiness, distended neck veins and congestion on upper half of body (superior vena cava obstruction
- There is no history of night time bones pain, paler of complexions and bone fracture on minor trauma
- There is no history of lumps and bumps in the body.
- No Hx of moon face, excessive hair on the face, chin and newly diagnosed DM & HTN (Cushing syndrome.
- no Hx of heat intolerance , tremor and loose motion(hyperthyroidism
- no Hx of constipation , colicky abdominal pain and increased thirst ,and psychological problems (hyperparathyroidism
- no Hx of tiredness all the time and fatigability(SIADH)
- **Metastasis:** From head to toe like;

Scanned with CamScanner

- CNS: Headache that is more severe in the morning, worsen with coughing & straining, fits and bilateral lower limb weakness.
- spinal cord no Hx of weakness in upper or lower limb
- Liver: Heaviness in the RHC with yellow discoloration of the eyes.
- Adrenals: There is no history of darkening of skins complexion with dizziness on standing from siting position. (Addison)
- Direct spread: To Rib or chest wall invasion, hoarseness of voice, dysphagia, SVC syndrome, Horner syndrome, Brachial plexus.
- Distant Mets: Lymph nodes, brain, bones, liver, adrenals
- CVS → Marentic endocarditis

- Complication related to chemo or radiotherapy.
- Para neoplastic complications

More common with small cell lung cancer

- Small cell lung carcinoma (SCLC)
  - SIADH
  - Lambert Eaton Syndrome (70%). Hx of patient present with dry mouth palpitations and proximal muscle weakness that improves with exercise
  - ACTH , Hx excessive hair growth on body, moon face and newly diagnosed DM& HTN (Cushing syndrome)
- Non- SCLC
  - Gynaecomostia → adenocarcinoma
  - ↑Calcium, ↑PTH, ↑ TSH, Clubbing and HPOA (check wrist tenderness)→ squamous cell ; hyperthyroidisms and hyperparathyroidism
  - SIADH, ↑ACTH, ANP→ Bronchial carcinoma.
- Para neo plastic Antibodies
  - Anti-Hu (causes painful neuropathy and sometime encephalomyelitis), Anti-YO (cerebellar degeneration), anti-RI (opsoclonus-myoclonus syndrome) these are anti-neuronal antibodies leads to cerebellar syndrome. (There is no history of dizziness or falling towards a particular side (Ataxia)
  - Pre-synaptic Voltage gated Calcium channel antibodies:
  - Lambert Eaton syndrome→ see above.

Now ask relevant

ITP and FAM-HUGS-FOSS-TV

Examination scheme

vitals followed by GPE including wasting of the small muscles of the hands, nicotine stain, JVP, jaundice, ptosis and miosis (Horner syndrome) axillary and cervical group of lymph nodes examination .(On examination, an old-thin lean and cachectic gentleman who has nicotine staining, clubbing of fingers and palpable supraclavicular lymph node that is 3-4 in numbers, hard in consistency , fixed ,non-tender and ---- cm in diameter).

- Examine back of the chest followed by front of the chest in detail(prominent veins due to

Scanned with CamScanner

SVO obstruction, sacra marks for lobectomy or pneumonectomy , see for effusion , collapse and mass in the lungs .

- Next, examine CVS for stigmata of infective endocarditis (Marentic), murmurs and pericarditis.
- Examine abdomen for any visceromegaly, ascites. Examine motor and sensory(for neuropathy) system, back for spinal tenderness, check cranial nerves (ptosis and miosis) and cerebellum (Para neoplastic degeneration), gait (look for Gower sign due to proximal myopathy)and check orthostatic hypotension (Mets to adrenals). At the end do fundaoscopy and look for papilledema that may signify brain metastases.
- Look for supportive findings of your differential diagnosis as well.

Present your case and Based on history and clinical examination

My clinical diagnosis or differentials are

- carcinoma lung
- pulmonary tuberculosis
- bronchiectasis
- (In addition, COPD leading to CA lung

Scanned with CamScanner

VIVA OF CA LUNG

How will you investigate this patient?

- Routine investigations

CBC (anemia) ESR &CRP, serum electrolyte (to look for SIADH and Addison), coagulation profile like PT, APTT, and INR for bleeding disorder and DIC, LFTs for liver involvement. CXR, Sputum for cytology, AFB and Gene Expert

- **Specific investigations**

Pleural fluid aspiration for routine examination and malignant cytology
CT chest with contrast, CT/MRI brain, bone scan and whole body CT or PET scan for metastases.
Biopsy or FNAC of accessible enlarged lymph nodes,
Pulmonary function tests including spirometery (FEV1) to assess perioperative complications and long-term pulmonary insufficiency following lung resection.
Fibropticbronchoscopy with biopsy for **central lesion** and for **peripheral lesion** CT guided biopsy, open lung biopsy, VATS and the latest Electromagnetic navigation transponders (EMTs).

What are the different routes /methods of biopsy for lung cancer?

- trans bronchial
- Fibrotic
- open
- CT guided
- VATS
- FNAC of lymph nodes
- trans esophageal biopsy
- Electromagnetic navigation biopsy
- Fluorescence bronchoscopy for luminal tumor

When and how to screening for CA lung?

annual screening with low-dose CT for smoking aged 50-80 who have at least a 20 either pack-year smoking Hx and who either currently smoke or have quit within the last 15 years.

What are the histological classifications of CA lung?

For staging and treatment bronchogenic carcinomas are divided into small and non-small cell carcinoma

- small cell carcinoma 13%, central and non-intraluminal
- non-small cell carcinomas
- squamous cell carcinoma 23% , often central and intra luminal .most common subtype in UK
- Adenocarcinoma 50%, present as peripheral nodules or mass. Most common subtype of lung cancer in USA.
- large cell carcinoma 1.3%

Scanned with CamScanner

,ionizing radiation

- Metals like arsenic, chromium, nickel and iron oxide.
- family Hx
- Certain lung diseases like COPD, interstitial lung disease and sarcoidosis.

What is the TNM staging of CA lung?

Small cell lung carcinoma has its own classification e.g. limited and extensive disease.

Limited disease (30%)

When the tumor is limited to unilateral hemi thorax and contralateral mediastinal nodes

Extensive disease (70%)

When the tumor extend beyond the unilateral hemithorax including pleural effusion.

A. How Would You Treat Small Cell Lung Carcinoma?

Limited

Cisplatin and etoposide (80-90% response) and thoracic radiation. Concurrent chemo and radio is the treatment of choice for limited tumor. Prophylactic cranial irradiation is recommended for limited disease due to high rate of brain metastasis.

mean 2-years survival rate is 20-40% and median survival is 15-20 months.

Extensive disease

Palliative chemo like cisplatin and etoposide and external beam radiation (60-80% response) is the recommended treatment for extensive disease. There is modest improvement in survival with addition of checkpoint inhibitor like atezolizumab or durvalumab to above mentioned chemotherapy agents. Early referral to a palliative care specialist is recommended. Palliative care like morphine for bone pain, thoracentesis, pleurodesis and pleural catheter for pleural effusion and stereotactic radiation therapy for limited brain metastases. mean 2-year survival is 5% while median survival is 8-13 months

B. How Would You Treat Non-Small Cell Lung Carcinoma (NSCLC)?

Treatment depends on TNM staging.

For FCPS internal medicine exam you need to memorized the below simplified TNM staging based treatment.

T = extent of the tumor, N nodal involvement, M distant metastases.

Extent of the tumor

T1 <3cm T1A tumor ≤ 1cm in the greatest dimension and T1B is > 1cm but ≤ 2cm in greatest dimension

T2 >3cm but ≤ 5cm. T3 >5cm but≤7cm. T4 >7cm.

Nodal involvement

- N 1 involvement of ipsilateral hilar, per bronchial and intrapulmonary nodes
- N2 involvement of ipsilateral mediastinal and/or subcarinal lymph nodes
- N3 involvement of contralateral mediastinal, hilar, scalene and supraclavicular nodes

Scanned with CamScanner

Distant Metastases

M1 simply signify distant Mets

- M1a=Separate tumor nodule's in a contralateral lobe tumor; tumor with pleural or pericardial nodules or malignant pleural or pericardial effusion
- M1b =single extra thoracic metastases in a single organ and involvement of a single no regional node
- M1c= multiple extra thoracic metastases in a single organ or in multiple organs.

- **Stage 1a** →T1N0M0 surgical resection like, lobectomy and if it cannot be tolerated than sublobar resection like wedge resection or segmentectomy. However if patients who are not candidates for surgery due to any reasons, than stereotactic body radiotherapy
- **Stage 1b**→ T2N0M0 and **stage II** T1-3 N0-N1 M0, surgical resection and chemotherapy like Cisplatin, etoposide and bevacizumab (Recombinant humanized monoclonal antibody to VEG).
- **Stage IIIa** T1-T4N0-N2M0 , resection + above mentioned chemo or resection + radiation therapy
- **Stage IIIb** same like IIIa but N3
- **Stage IV** is M1.

For stage, IIIa and IV NSCLC treatment option include targeted therapy, cytotoxic chemotherapy and immunotherapy (checkpoint-inhibitors). In these stages only palliative chemo, radio or immunotherapy.

Enumerate few important immunotherapy (checkpoint-inhibitors Recent Advances) agents for NSCLC.

- ALK+ → Lorlatinib crizotinib, alectnib and ceritinib
- EGFR+ → Osimertinib. afatinib,dacomitinib
- NTRK+ → Larotrectinib or entrectinib
- PDL-1+ → Pembrolizumab ,atezolizumab
- k-ras+ →Sotorasib
- BRAF+ → Dabrafenib/trametinib etc

What are the advantages of checkpoint-inhibitors?

It improves survival in NSCLC.

What are the adverse effects of checkpoint-inhibitors?

May leads to inflammatory response in various organs like thyroiditis, pneumonitis and hepatitis and type 1 diabetes.

What is the prognosis of lung cancer?

Overall 5-year survival rate for lung cancer is approximately 20%. Predictor of survival includes tumor type, stage of the disease, molecular profile, and patient performance status. In NSCLC adenocarcinoma has best prognosis while undifferentiated has the worst.

What are the contraindications to surgery in NSCLC?

- Stage IIIb or IV (metastatic diseases)
- FEV <1.5 (poor respiratory reserve)

Scanned with CamScanner

- Malignant pleural effusion
- Tumor near hilum
- Superior vena caval obstruction. it is an oncological emergency and warrants immediate management like iv high dose steroid+ anticoagulation and then refer for proper treatment like stenting or radiation.
- Vocal cord paralysis (signify distant Mets).
- Poor general health like age> 70 and premorbid like IHD.

What are the markers of lung cancer?

Napsin A > thyroid transcription factor1

How would you treat secondaries in the lung?

Treat the underlying or primary tumor. Common sites of primary tumor may be breast, thyroid, kidney, ovaries and uterus etc.

How would you treat the mesothelioma?

Chemotherapy is the mainstay of treatment and Chemo agents like Cisplatin or carboplatin /pemetrexed with or without bevacizumab (anti-VEGF) or Nivolumab (checkpoint-inhibitor) with cytoreductive surgery for localized disease that is amenable for macroscopic resection. Surgical options for localized disease include pleurectomy and decortications. In advanced unresectable mesothelioma, palliative chemotherapy like Cisplatin and pemetrexed and bevacizumab and Nivolumab has improved overall survival. Other palliative care like drainage of pleural effusion or pleurodesis, radiation therapy or even surgical resection may be considered. 5-year survival is 5-10%.

How to distinguishing haemoptysis from haematemesis and nasopharyngeal bleeding		
Favours haemoptysis	Favours haematemesis	Favours nasopharyngeal bleeding
Mixed with sputum	Follows nausea	Blood appears in mouth
Occurs immediately after coughing	Mixed with vomitus; follows dry retching	

What is non –metastatic paraneoplastic features of CA lung?

Scanned with CamScanner

Endocrine

- Ectopic ACTH secretion
- SIADH
- Hypercalcemia
- Carcinoid syndrome
- Gynenomastia

Neurological

- Polyneuropathy
- Myelopathy
- Cerebellar degeneration
- Lambert-Eaton syndrome

Scanned with CamScanner

APPROACH TO DRY COUGH (Due to DPLD esp. ILD)

PC

- SOB (see approach to SOB) or
- Dry cough

(Apply ODPARAV OF SOB or COUGH .....

My patient presented with cough that is gradual in onset, progressive in nature and 6-8 months in duration. Initially cough was during severe exertion like walking up-stair but for the last..... months/weeks my patient suffer cough bouts on mild to moderate exertion like walking on flat ground and sometime while lying in the bed at night. Cough is mostly dry but sometime with scanty mucoid sputum production that is difficult to expectorate. Cough is worsening by activities and initially relieved by rest and cough syrup but now it is partially relived by cough Syrup. There is no blood in the sputum. It is associated with SOB on exertion

However, there is no Hx of...

Now exclude imp D/Ds of dry cough

- **cough variant asthma**

There is no HX Dry cough that is more at night & early morning associated with whistling sounds and seasonal variation of these symptoms

- **COPD**

There is no Hx of smoking or exposure to biomass, fuel, factory, fume and dust

- **Sarcoidosis**

There is no Dry cough associated with painful skin lesion

- **ILD**

Long case here and diagnosis of exclusion .see below

- **GERD**

There is no Hx of dry cough associated with retrosternal burning sensation and regurgitation of food content into mouth.

- **ACE & B-blocker(drug induced cough)**

There is no Hx of intake of above medication for ..... (Mention indications)

- **CA LUNG**

There is no Hx of lumps& bumps, change in the quality of voice, decreased appetite and weight loss.

- **Connective Tissue Disorder (CTD)**

There is no Dry cough associated with joint pain, oral ulcer, rash and tightening of the skin

- **Upper airway syndrome**

There is no HX of repeated throat clearness, postnasal drip, nasal congestion, nasal drainage, facial pain on touch and tickling sensation in throat

DDS of cough with scanty sputum (1-2 teaspoons) /productive cough

- **Bronchiectasis**

Scanned with CamScanner

Hx of cough associated with foul smelling sputum production that expectorates at certain position.

- **Pneumonia**

Cough associated with high-grade fever and rusty sputum production

- **Lung abscess**

Cough associated with high-grade fever rigors and chills in alcoholic,/ in IV drug abuser, and or in those using immunosuppressive medication

- **Foreign body**

Hx of cough associated with aspiration of foreign body,

- **Malignancy**

Hx of lumps & bumps in the body, weight loss, decreased appetite

- **Autoimmune disorder**

Cough associated with joint pain, oral ulcer, hair fall, photosensitivity and skin tightening.

- **Vasculitis like Wagner and churg-strauss**

Hx of palpable skin rash, blood in sputum or urine and joint pain

- **Chronic bronchitis**

Hx of chronic persistent cough associated with SOB and wheezy chest that is worse during winter.

- **Heart failure**

Hx of SOB on exertion and while lying flat that improve in prop-up position, disturbed night sleep ,distended neck veins and lower limb swelling .

- **TB (TB** is a less likely differential in dry cough)

Hx of weight loss, night-time sweating, low-grade fever and past or contact Hx of TB

- If patient presents with dry/scanty cough, always first exclude differentials of dry cough followed by productive cough and vice versa

CARE/RECA of ILD

- No HX of exposure to farm, factory , mines, particles and birds (occupational lung diseases)
- no Hx of butterfly rash on face, hair loss , oral ulcers , arthritis and tightening of skin (Connective tissue disorder)
- no Hx of rash involving eyelids ,knuckles of hands, neck and, proximal muscle weakness and painful muscles (Dermatomyositis and polymyositis)
- no past Hx of pulmonary tuberculosis
- no Hx of exposure to radiation or bone marrow transplant
- no Hx of exposure to chemotherapy or drugs like amiodarone, cyclophosphamide, bleomycin , methotrexate(Drug induced lung fibrosis)
- no Hx of painful lesion on shin , parotid swelling associated with these symptoms (sarcoidosis)
- No Hx of palpable skin rash, weight loss, joint pain and blood in sputum and urine (vasculitis).
- and idiopathic
    - Idiopathic pulmonary fibrosis is diagnosis of exclusion (exclude major causes and

Scanned with CamScanner

if no cause is found than it is idiopathic pulmonary fibrosis).

COMPLICATIONS OF ILD

- **Right heart failure** no Hx of engorged neck veins, abdominal distension & painful right hypochondrium and pitting pedal edema
- **Cyanosis** no Hx of bluish discoloration of lips, nails, skin and mucous membrane
- **Pneumothorax,** no Hx of sudden severe chest pain that was made worse by respiration and relived by needle aspiration or chest drain
- **Repeated chest infection & pleural effusion(due to primary disease or immunosuppressive medications)** no Hx of recurrent chest infection
- **CO_2 Narcosis,** no Hx of morning headache, tremors and confusion
- **CA LUNG** no Hx of lumps and bumps, weight loss, change in the quality of voice and blood in the sputum.
- **Steroids adverse effects** no Hx of moon like face, weight gain, proximal muscle weakness, newly diagnosed HTN, DM and excessive hair on face.

ITP OF ILD

Ask about relevant investigation like baseline, HRCT, Bronchoscopy, Biopsy and investigations for secondary causes of ILD as mentioned in viva portion. Ask about treatment like corticosteroids and immunosuppressive therapy its dose, duration and improvement in symptoms by that particular therapy and possible complication as well .

Now **Ask Relevant PAM-HUGS-FOSS-TV**

EXAMINATION

Vitals and GPE(in GPE search for clues of the cause of lung fibrosis) old, thin lean emaciated man in obvious respiratory distress having nicotine stained clubbed fingers of both hands (25-50% ,absence of clubbing doesn't exclude lung fibrosis), also look for joint deformity , skin rash ,tremors ,striae , purpura , puckering of skin around mouth , palpable nodes , JVP(normal/raised) , peripheral & central cyanosis, jaundice, anemia and pitting edema).

RESP →follow standard protocol of examination like

Normal shape chest with indrwaing of lower part of the chest and patient is in respiratory distress with RR is almost in range of 25-30 breathing per minute. There is reduced chest expansion <3cm, trachea is central in position, vocal fremitus is reduced (normal) at bases and apex beat is in 5^{th} intercostal space in midclavicular line. Percussion note is impaired (normal) at the bases of chest. Breath sound are vesicular with reduced intensity .There are bilateral basal fine crackles that do not alter with cough.

CVS and Abdomen →Look for right heart failure signs (like parasternal heave, loud P2, tender hepatomegaly, splenomegaly and ascites

MSK→ look for proximal myopathy induced by steroid

Scanned with CamScanner

Based on history and examination my diagnosis or differential diagnoses are

- DPLD most likely idiopathic interstitial fibrosis
- Post-TB fibrosis /fibrosis due to ....
- CA lung

VIVA OF ILD

How will you investigate this patient?

- **Baseline investigations**

  CBC (lymphopenia in sarcoidosis, ↑eosinophilia in pulmonary eosinophilia's and drugs ↑neutrophilia in hypersensitivity), ESR, CRP, LFTS (congestive Hepatopathy), serum calcium, and ABGs (Type 1 rasp failure) and CXR (see below)

- **specific investigations**
  - autoimmune profile /ENA profile like ANA, RA , P &C ANCA, anti Jo-1 antibodies , antiMI2ntibodies and Anti-GBM antibodies
  - Creatine Kinase ,LDH
  - Serum ACE ,Serum calcium , urinary calcium excretion (and liver biopsy) for sarcoidosis
- **IMAGING STUDY**

  Chest-x-ray

  Typically small lung volumes with reticulonodular shadowing but may be normal in early or limited disease

High –resolution computed tomography (HRCT)

Combinations of ground glass changes, reticulonodular shadowing, honeycomb cysts and traction bronchiectasis depending on stage of the disease. Usually two predominant patterns

- Honeycombing → usual interstitial pneumonia (idiopathic pulmonary fibrosis)
- Ground glass appearance →non –specific interstitials pneumonia and others.

- **Pulmonary Function Test**
  - restrictive ventilatory defect (FEV1/FVC > 70
  - reduced lung volume , gas transfer factor and gas transfer coefficient
  - exercise –related fall in SaO2
- **Bronchoalvolar Lavage (BAL)**

  Differential cell counts may point to sarcoid and drug –induced pneumonitis, pulmonary eosinophilia's, hypersensitivity pneumonitis, (lymphocytosis) cryptogenic organizing pneumonia and to exclude infection.
- **Bronchoscopy with lung biopsy**

  It is rarely needed like in case of diagnostic uncertainty of infection, malignant process and atypical features.
- **video-assisted thoracoscopic lung biopsy (in selected cases)**

Scanned with CamScanner

Allows pathological classification, asbestoses, silicosis and vasculitis etc

What is the Pathogenesis of ILD?

Endothelial injury that leads to inflammation and fibrosis

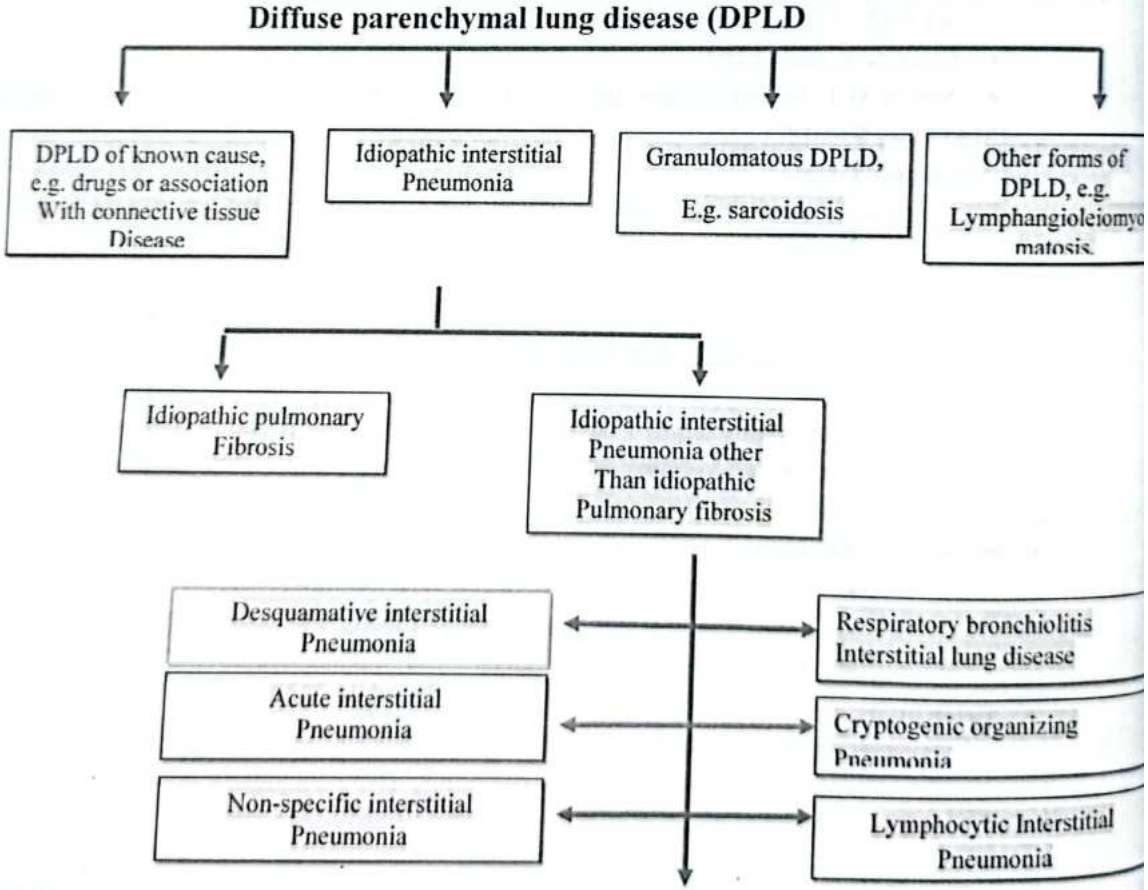
What Is DPLD

It is heterogeneous group of conditions affecting the pulmonary parenchyma e.g. intertitium and or alveolar lumen. Previously it was called interstitial lung diseases (ILD)but this signified that pathology affects just intertitium and that is why DPLD is preferred term that denotes pathology of intertitium and /or alveolar lumen or both.

What is idiopathic Pulmonary Fibrosis?

It is a pathological condition characterized by progressive fibrosing interstitial pneumonia of unknown cause, occurring in adult, and associated with the histological or radiological pattern of usual interstitial pneumonia. **How Will You Classify DPLD?**

Classification of DPLD


Diffuse parenchymal lung disease (DPLD
DPLD of known cause, e.g. drugs or association With connective tissue Disease
Idiopathic interstitial Pneumonia
Granulomatous DPLD, E.g. sarcoidosis
Other forms of DPLD, e.g. Lymphangioleiomyomatosis
Idiopathic pulmonary Fibrosis
Idiopathic interstitial Pneumonia other Than idiopathic Pulmonary fibrosis
Desquamative interstitial Pneumonia
Acute interstitial Pneumonia
Non-specific interstitial Pneumonia
Respiratory bronchiolitis Interstitial lung disease
Cryptogenic organizing Pneumonia
Lymphocytic Interstitial Pneumonia

ıat is the most common type of DPLD?

›pathic pulmonary fibrosis also called usual interstitial pneumonia.

Scanned with CamScanner

What are the causes of DPLD?

Most common cause is idiopathic

Other causes include

- **DRUGS**

Like Amiodarone, Cyclophosphamide, Bleomycin, Methotrexate and Nitrofuraontoin

Radiation fibrosis

Granulomatous disorder

Sarcoidosis

Rheumatological disorders

Rheumatoid arthritis

Systemic sclerosis

Systemic lupus erythematosus

Polymyositis

Dermatomyositis

Mixed connective tissue disease

Eosinophilic lung disease

Aspergillosis

Drugs (Nitrofuraontoin, imipramine, and sulfasalazine)

Inhaled agents

Silicosis and bryliosis

Extrinsic allergic alveolitis

Vasculitis

Wagner, Churg-strauss etc.

What are the stages of DPLD?

The stages of DPLD are as follow

Stage of ground glass opacity

Stage of reticulonodular shadow

Stage of streaky fibrosis

Stage of honeycombing

How would you treat Idiopathic lung Fibrosis (ILD)?

- Counselling regarding the nature of disease
- Quit smoking
- **Vaccination for influenza and pneumococcus**
- Bronchodilators
- LTOT if indicated (same indication as for COPD/ Cor Pulmonale
- Low dose steroids 1-2mg/kg/day for 2months if responsive than tapper the dose continue for 2years and if not responsive after 2months than switch to anti-fibrinolytic drugs like perfenidone (inhibit transforming growth factor TGF-beta) 267 mg TDS & nintedanib (tyrosine kinase inhibitor) 150mg BD .It decreases disease progression and decline in lung function but has no survival benefits and does not improve quality of life (SOB & Cough). It

Scanned with CamScanner

should be stopped when more than 10% decline in lung function occur during first year of treatment.

- Treat pulmonary hypertension and cor-Pulmonale.

What precaution should be observed while taking perfenidone?

Direct exposure to sunlight and use photo protective clothing and high –protection sunscreens

What are the indications of LTOT?

Same as for COPD/ and or Cor Pulmonale.

What are the steroid responsive types of DPLD?

Except usual interstitial Pneumonia (UIP) also called idiopathic pulmonary fibrosis other types of DPLD are responsive to steroids.

What is the definitive treatment of IPF?

Lung transplantation or heart-lung transplantation in case of pulmonary hypertension and this sort of treatment has survival benefits. 1 year survival post –transplantation is 75% while 5 years survival is 50%.

How will you treat lung fibrosis other than IPF?

By treating the underlying cause

What are the poor –prognostic factors of ILD?

Young age, rapid progression of the disease, pulmonary hypertension and right heart failure.

What do you know about Acute interstitial Pneumonia or Hamman –rich syndrome?

It is an acute form of idiopathic interstitial pneumonia characterized by acute onset shortness of breath followed by rapid development of respiratory failure .half of the patient has viral syndrome preceding this syndrome .it has high initial mortality as 50-90% dies within 2 months after the diagnosis . it has specific radioaghrapic pattern characterized by diffuse bilateral airspace consolidation with areas of ground-glass attenuation on HRCT. It clinical course is indistinguishable from that of idiopathic ARDS. if patient survived the initial phase than it is non-progressive. Management is largely supportive

What are the conditions that mimic diffuse parenchymal lung disease?

- Infection

Tuberculosis, viral pneumonias, mycoplasma pneumonaie, pneumocystis jiroveci, fungal infection and parasite like filariasis

- malignancies

Leukemia & lymphoma, bronchoalvelolar carcinoma, lymphangitic carcinomatosis

- pulmonary edema
- Aspiration pneumonitis

What are the causes of predominantly upper and lower lobe fibrosis?

Upper lobe Fibrosis

(S-CHART)

Silicosis and sarcoidosis

Coal workers pneumoconiosis

Scanned with CamScanner

Histiocytosis
Ankylosing spondylitis
ABPA
Radiations
Tuberculosis
Lower lobe fibrosis
(RASCO)
Rheumatoid arthritis
Asbestosis
Scleroderma
Cryptogenic fibrosing alveolitis
Others (drugs like busulphan, amiodarone, bleomycin and methotrexate

What is the bedside test for severity of lung fibrosis?

Bedside 6-minute walk test.

What are the Recent Advances in ILD?

Recombinant human pentraxin-2 and Cavolin (anti-inflammatory agents) are under study.

New drug for ILD

Pamrevlumab (monoclonal –antibody for ILD)

Tell me about the prognosis of ILD

The natural history is usually one of the serial declines. A median survival of 3 years is widely quoted; the rate of disease progression varies considerably, however, from death within a few months to survival with minimal symptoms for many years.

Comparison of the chest signs in common respiratory disorders

Disorder	Mediastinal displacement	Chest wall movement	Percussion note	Breath sounds	Added sounds
Consolidation	None	Reduced over affected area	Dull	Bronchial	Crackles
Collapse	Ipsilateral shift	Decreased over effected area	DULL	Absent Or reduced	Absent
Pleural effusion	Heart displaced to opposite side trachea displaced only if massive	Reduced over affectedy area	Stony dull	Absent over fluid, may be bronchial at upper border	Absent, pleural rub may be found above effusion

Scanned with CamScanner

Pneumothorax	Tracheal deviation to opposite side if under tension	Decreased over affected area	Resonant	Absent or greatly. reduced	Absent
Bronchial asthma	None	Decreased symmetrical	Normal or decreased	Normal or reduce	Wheeze
Interstitial pulmonary fibrosis	None	Decreased symmetrically (minimal)	Normal unaffected by cough or posture	Normal	Fine, late or pan-inspiratory crackles over affected lobes

Causes of hypersensitivity pneumonitis

Disorder	Source	Antigen/agent
Formers lung	Mouldy hay, straw. grain	Saccharoplyspora rectivirgula (formerly) micropolyspora faeni aspergillus fumigatus
Bird fancier,s lung	Avian excreta, proteins and feathers	Avian serum proteins
Malt worker,s lung	Mouldy maltings	Aspergillus clavatus
Cheese worker,s lung	Mouldy cheese	Aspergillus clavatus penicillium casei
Maple bark stripper,s lung	Bark from stored maple	Cryptostroma corticale
Saxophone player,s lung	Reed of any wind instrument	Fusarium spp. Penicillium spp. Cladosporium spp.
Byssinosis	Textile industries	Cotton, flax, hemp dust
Inhalation (humidifier) fever	Contamination of air conditioning	Thermophilic actionmycetes

Scanned with CamScanner

APPROACH TO PRODUCTIVE COUGH (Due to Bronchiectasis)

P/C

Worsening of productive cough for .....duration

HOPI(ODPARAV)

My patient who has been suffering from chronic cough for the last one and half year now presented with worsening of cough for the last 20 days .Cough is productive in nature almost 4-6 TSF in quantity, foul-smelling & mucopurulent more at the morning and expectorate at certain position and very rarely stained with fresh blood that is half TSF in quantity (comment on frequency, volume, color and quantity of sputum production).

it is associated with (right sided)chest pain that was gradual in onset , mild to moderate in intensity . dull in character and non-radiating worsen by coughing and relived with pain reliving medication (Productive cough may be associated with SOB in most of the time so you should briefly described SOB like shortness of breath was slow in onset, progressive in nature as initially it was on severe exertion like climbing the stair but for the last 20 days it is on moderate exertion like walking more than 10 minutes on flat ground, SOB exacerbate on exertion and relived by rest .patient denied shortness of breath while lying flat or disturbed sleep at night.) . HX dates back one and half year when my patient presented with cough to a local doctor (now briefly described how the patient was investigated , diagnosed and treated with recommendation of chest physiotherapy etc)

Now exclude important relevant DDS of productive cough like

- **Bronchiectasis**

Long case here

- **Pneumonia**

There is no Hx of associated with high grade fever with rigors & chills and rusty sputum production

- **Lung abscess**

Cough associated with high grade fever rigors and chills in alcoholic,/ in IV drug abuser, and or in those using immunosuppressive medication or having poor oral hygiene or patient who has loss of consciousness .

- **Foreign body**

There is no of Hx of cough associated with aspiration of foreign body,

- **Malignancy**

No Hx of lumps & bumps in the body, weight loss, decreased appetite

- **Autoimmune disorder**

There is no HX of Cough associated with joint pain, oral ulcer, hair fall, photosensitivity and skin tightening.

- **Vasculitis like Wagner and churg-strauss**

No Hx of palpable skin rash, blood in sputum or urine and joint pain

- **Chronic bronchitis**

No Hx of chronic persistent cough associated with SOB and wheezy chest that is worse during

Scanned with CamScanner

winter.

- **Heart failure**

no Hx of SOB on exertion and while lying flat that improve in prop-up position, disturbed night sleep ,distended neck veins and lower limb swelling .

- **TB**

There is Hx of weight loss, night- time sweating and low-grade fever.
If you do have time exclude FEW DDS OF dry Cough (see DPLP section) too.

CARE /RECA of Bronchiectasis

- **ABPA**

There is no HX of asthma that is not responding to inhaler therapy.

- **Suppurative pneumonia**

There is no Hx of high-grade fever, chest pain with rusty color sputum production

- **Inhaled foreign body**

There is no Hx of aspiration of foreign body during childhood

- **Bronchial tumor**

There is no HX of weight loss, lumps and bumps in the body, change in the quality of voice and difficulty in swallowing

- **Yellow nail syndrome**

No Hx of yellow discoloration and/or dystrophy of nails, lower limb swelling and pleural effusion.

- **Kartagner syndrome**

No Hx of recurrent sinusitis (facial pain , postnasal –drip), dextrocardia associated with these complaints

- **Young syndrome**

Patient denied any Hx of infertility (in the family too

- **Hypogammaglobulinemia (IgA & IgG)**

No Hx of recurrent chest infection or chronic diarrhea

- **Recurrent childhood infection**

There is no Hx of repeated chest infection in childhood

- **Cystic fibrosis**

No Hx of repeated chest infection, delayed growth, rectal prolapse, chronic foul smelling diarrhea and diabetes.

- **RA**

There is no HX early morning pain and stiffness of small joints of both hands and feet, or deformity

- **IBD**

Recurrent abdominal pain associated with blood in loose stool and mouth ulcer

- **Sjogren syndrome**

There is no Hx of dry eyes, dry mouth and numbness.

- **Transplantation of solid organ**

Scanned with CamScanner

No Hx of transplant

However, there is Hx of pulmonary tuberculosis ...years back. Now tell how it was diagnosed, duration of treatment and any complication of TB and its treatment briefly .

- **exclude few important DDs according to your time management**

Now ask about complications of bronchiectasis

- **Right heart failure**
  Hx of engorged neck veins, abdominal distension, yellow discoloration of sclera and pedal edema.
- **Respiratory failure**
  Hx of ICU admission, invasive or non-invasive ventilation
- **CO2 narcosis**
  Hx of early morning headache, confusion and irritability
- **Pneumothorax & pleural effusion**
  Hx of sudden severe chest pain that exacerbate with breathing and drainage of fluid from chest cavity
- **Massive hemoptysis**
  Hx of large amount of blood in sputum that was difficult to control
- **Metastatic brain abscess**
  Hx of focal neurological deficit associated with high-grade fever.
- **amyloidosis**
  Hx of enlarge tongue, SOB on exertion and lying flat and disturbed night sleep (or any other organ damage like periorbital swelling or gen body swelling due Nephrotic syndrome 2 amyloidosis)
- **aspergilloma→**

Now ask about relevant ITP.

Relevant investigation, treatment and procedures if any (see viva section) .

RELEVANT PAM-HUGS-FOSS-TV

past Hx is significant for pulmonary TB and ask detail regarding what were the symptoms or signs that led to diagnosis of TB and what investigation were carried out at that time like sputum examination or CXR, aspiration of pleural effusion and ask about treatment and complication if you missed or skip it in CARE section of history . Ask recurrent infection exacerbations) that had leads to hospital admissions .Ask family or personal Hx for fertility problems .also ask about immunization HX.

Examination

GEN look

Vitals →GPE specifically look for clubbing, nicotine staining and tremors (due to beta -agonist or CO2 narcosis).

Examine resp system as per standard protocol and look for below findings

Scanned with CamScanner

- chest expansion is reduced ,percussion note is resonant (or dull) , inspiratory coarse crakles that alter on coughing and vocal resonance is reduced or normal
- Physical sign in the chest may be unilateral or bilateral .if the airways does not contain secretions and there is no associated lobar collapse, there may be no abnormal physical signs.
- When there are large amounts of sputum in the bronchiectatic spaces, coarse crakles may be heard over the affected areas.
- collapse with retained secretions blocking a proximal bronchus may lead to locally diminished breath sounds , while advanced disease may cause scarring and overlying bronchial breathing

CVS

For sign of pulmonary hypertension and right heart failure and dextrocardia

Abdomen

For hepatomegaly and ascites 2 to right heart failure

Neurological examination

For any neurological deficit

Fundaoscopy

Papilledema and choroidal tubercles (on posterior pole due to reactivation of TB) and look for orthostatic hypotension (2 to TB or steroid withdrawal.

Based on Hx and examination my clinical diagnosis or/ differential diagnosis are

1. post-TB bronchiectasis
2. lung abscess
3. lung infection
    - reactivation of TB
    - chronic(non-resolving) pneumonia

Scanned with CamScanner

VIVA OF BRONCHIECTASIS

How would you investigate this patient?

- **CBC with ESR** →Eosinophilia, polycythaemia/anemia and neutrophilic leukocytosis
- **Sputum gram staining and culture** →culture may reveal in most of the cases Haemophilus influenzae from non-cystic fibrosis patient with bronchiectasis while other pathogens are pseudomonas, Staph aureus, fungi such as Aspergillus and various mycobacteria)
- **Chest-X-ray**→ may be normal during early stage while in advanced stage it may show thickened and dilated bronchi that may appear as tram –track or ring-like marking, focal consolidation and multiple small cavities.
- **X-ray PNS** →**in** kartagner s syndrome)
- **HRCT** (single best investigation of choice for bronchiectasis)

HRCT slide are 1-2mm thick having sensitivity of 90%while routine CT is 10mm thick slices (sensitivity of 60- 80%) that can miss bronchiectatic changes

- **Pulmonary function test**→ PFTS may shows obstructive lung disease in moderate to severe diseases (very rarely restrictive pattern in advanced stage
- **Immunoglobulin quantification**
- **Saccharin screening test and nasal nitric oxide**→ for patients suspected of having a ciliary dysfunction syndromes.
- **Sweat chloride test** for cystic fibrosis.
- **Genetic testing**
- **Bronchoscopy** →to locate the site of bronchoscopy
- **Autoimmune profile** → RA , ANA
- **Aspergillus precipitating antibody or skin prick test if** →ABPA is suspected
- **Urine examination for** proteinuria in longstanding bronchiectasis if amyloidosis is being suspected
- **Ultrasound Abdomen**→ if situs inversus is suspected

What is bronchiectasis?

It is an abnormal permanent dilatation of one or more bronchi with destruction of bronchial wall proximal to terminal bronchioles

What are the types of bronchiectasis?

1. Saccular or cystic
2. Cylindrical
3. Fusiform

What is the commonest site of bronchiectasis?

Left lower lobe and lingula

What is bronchiectasis sicca or dry bronchiectasis?

It is a type of bronchiectasis where cough is non-productive but often associated with recurrent hemoptysis. It is most commonly due to tuberculosis.

Scanned with CamScanner

Tell me the condition in which predominantly upper lobe is involved

Bronchopulmonary aspergillosis and tuberculosis

What is the clinical triad of bronchiectasis?

- Chronic productive cough
- Clubbing
- Coarse crakles on lung auscultation

What is the mechanism of hemoptysis in bronchiectasis?

Hemoptysis occurs due to friable bronchial arteries that slough up.

What is the bedside test in bronchiectasis?

If sputum is kept in a glass or bottle, there are three layers

Upper→ frothy

Middle →thick or liquid

Lower →sediment that contain debris and bacteria

What are the most common organisms isolated from bronchiectasis patients

Non-cystic fibrosis patient → Influenzae

Cystic fibrosis patient → pseudomonas > s. aureus

How would you guide this patient for treatment?

- **Explain nature of the disease**

This is a permanent disease as your air pipes are permanently dilated so your problem will stay and cannot be cured but some measures can be taken as listed below that help you get better and it may help you spend a normal life.

- **Advise Exercise** for sputum expectoration like ballooning, yoga and long deep breathing
- **Postural drainage** if you have right sided affected than keep it up and percuss that part with fist by your family member 2-3 times daily particularly in early morning .
- **Antibiotic therapy** antibiotic therapy should be guided by prior sputum smear and culture , however if specific bacterial pathogen cannot be isolated than empirical therapy from any of the following groups like penicillin, quinolones and 2nd or 3rd generation cephalosporin may be used for 10-14 days while inhaled antibiotic like tobramycin in cystic fibrosis patient .
- **Preventive antibiotic therapy** for recurrent exacerbation, preventive macrolide therapy (Azomax 250mg OD for one year) has been found to decrease the frequency of exacerbations.
- **Frank hemoptysis** the following may be advised to stop bleeding like bronchoscopy, embolization of the bleeding vessel and surgical resection if predominantly upper lobe is involved in a young patient.
- **Vaccination** against H-influenzae, strep pneumonaie

What do you know about lung abscess in bronchiectasis?

Common site upper lobe → posterior segment

Lower lobe →superior/basilar segment

Enumerate organism causing lung abscess

Scanned with CamScanner

Anaerobes like bacteriodes fragilis, peptostreptococcus, and fusibacterium and prevotella melaninogenica

What is the treatment of lung abscess?

medication of choices are directed at anaerobic organisms or facultative anaerobic streptococci and include a beta lactam /lactamase inhibitor combination , carbapenems or clindamycin for example IV augmentin 1g BD and clindamycin 600mg TDS and when symptoms improve than switch to oral 300mg QID.

2nd line therapy is combination of penicillin and metronidazole for minimum 3 weeks (exact duration is controversial) or unless the abscess cavity has resolved on imaging.

What are the complications of lung abscess?

Rupture into pleural cavity (treated by thoracic surgeon)
Pneumothorax
Fistula
Empyema (treated by chest intubation)

How would you treat abscess resistant to antibiotic

While large or non -resolving abscess needs surgical intervention like percutaneous drainage, segmentectomy, lobectomy or pneumonectomy.

What are the causes of multiple lung abscesses?

Klebsiella
Staph aureus, fungus and
Amebiasis

What is the significance of sputum C/S?

No significance because we do not do C/S for anaerobes due to oral contamination. Instead, we do broncospic washing / brush, Trans bronchial or Tran's thoracic aspiration or pleural fluid aspiration.

What are the CXR finding in bronchiectasis?

Chest X-ray PA view (may be normal during early stage) may show
Ring with clear center (like honeycomb)
Ring with or without fluid level, may be multiple (cystic bronchiectasis)
Linear streaks (tram line)
Thick bronchi signet ring or patchy opacity.
Cavity with air fluid level with peripheral consolidation

Tell me the syndromes associated with bronchiectasis

- Young syndromes
- Kartagner syndrome (Triad of dextrocardia, bronchiectasis and sinusitis or frontal sinus agenesis)
- Cystic fibrosis
- Yellow nail Syndromes.
- Swyer-James-MacLeod syndrome → as result of childhood bronchiolitis obliterans

What are the respiratory causes of clubbing?

Scanned with CamScanner

Bronchiectasis
Lung abscess
Empyema thoracis
Bronchial carcinoma
Mesothelioma
Interstitial lung disease

What are the causes of coarse crepitations altered after coughing?

Bronchiectasis
Lung abscess
Consolidation (resolution stage)
Pulmonary edema

What are the causes of unilateral basal crepitations?

Lung abscess
Bronchiectasis
Consolidation
Pulmonary fibrosis

What is the Prognosis of bronchiectasis?

Poor

High morbidity and low mortality

Scanned with CamScanner

CYSTIC FIBROSIS (CF)

Mode of inheritance

Autosomal recessive

What are the clinical features of CF?

In NEONATE

Failure to thrive, meconium ileus, meconium ileus and rectal prolapse

Children and adult

Respiratory features

Like recurrent chest infection, features of bronchiectasis, lung collapse, respiratory failure, otitis media, sinusitis, nasal polyps, lung collapse and resp failure or cor –Pulmonale in advanced stage.

Abdominal Features

Malabsorption or steatorrhoea due to pancreatic insufficiency
Secondary biliary cirrhosis and portal hypertension
Cholesterol gallstones
Distal intestinal obstruction syndromes (meconium ileus equivalent syndrome
Increased incidence of peptic ulceration and GI malignancy

Other features

CF related DM

Male infertility (due to failure of development of vas deference) while 20% of female with cystic fibrosis are infertile
Delayed puberty and skeletal maturity
Arthritis, osteoporosis
Cutaneous Vasculitis
Clubbing with hypertrophic osteoarthropathy
Low body mass index

How will you investigate (Diagnose) this patient?

Routine investigations

CBC, LFTs, RFTs.
Throat swab and sputum culture (H influenzae, P aeruginosa, S aureus and Burkholderia cenocepacia
X-ray chest (hyperinflation and bronchiectasis and pneumothorax
Spirometery (shows mixed obstructive and restrictive pattern
Faecal fat analysis
Ultrasound abdomen for liver cirrhosis

Specific Investigations

Blood immunoreactive trypsin levels (for screening purpose in newborn)
Quantitative pilocarpine inotophoresis sweat test → Cl > 60 mEql/L on two occasion (normal range is < 30mEq /L)
Abnormal potential difference
Strong clinical suspicion but Cl test negative 2 times than do

Scanned with CamScanner

CFTR genetic analysis (on chromosomes 7)

How will you treat this patient?

Gen measures like

Nutritional support and fat-soluble vitamins

Psychosocial support

Vaccination against influenza and pneumococcus

Advice to must quit smoking

Screening of family members and genetic counselling

Resp problems management

- **Airway clearance & reduction of lower respiratory secretion by**

Regular chest physiotherapy, positive expiratory pressure or flutter valve breathing devices, inhaled bronchodilator and mucolators.

- **Inhaled recombinant human deoxyribonuclease** (rhDNase, dornase-alpha, it Cleves extracellular DNA in sputum decreasing it viscosity) 2.5mg nebulized dose daily in long-term improves FEV1 and reduces the risk of cystic fibrosis related respiratory exacerbation and need for intravenous antibiotic.
- **Inhalation of hypertonic saline** (7%) help clear mucous from airway and small improvements in pulmonary function
- **Treatment of respiratory infection**

Short-term antibiotics to treat active resp infection base on report of culture and sensitivity. S aureus and P aeruginosa are commonly present while H influenzae, Stenotrophomonas maltophilia and B cenocepacia are occasionally isolated.

Long-term antibiotic therapy like azithromycin has immunomodulation effect and various inhaled antibiotics like tobramycin, aztreonem, and colistin etc. two to three times a day help slow disease progression and reduce exacerbation for P aeruginosa positive patient.

- ***CFTR modulators*** drugs like ivacaftor, lumacaftor, and tezacaftor and elexacafftor .these medication are indicated for patients with specific CFTR mutations .these medicine works by increasing the duration of channels opening time once activated.
- ***Treatment of complication like cor-Pulmonale*** like diuretics and oxygen
- ***Lung transplantation*** The only definitive treatment for advanced cystic fibrosis
- ***GI related problems management***

Pancreatic enzymes (CREON) for pancreatic insufficiency

Insulin for diabetes

Acute abdomen due to intestinal obstruction as per standard protocol like nothing by mouth, IV fluid and nasogastric suctioning etc

Ursodeoxycholicacid for impaired liver function and liver transplantation in cirrhosis

- **Miscellaneous**

Treatment for osteoporosis, infertility, sinusitis, vasculitis and arthritis

Scanned with CamScanner

What is the prognosis of cystic fibrosis?

Median survival age is 39-year

Death occours from pulmonary complications (e.g. pneumonia, pneumothorax) or as a result of terminal chronic respiratory failure and cor –Pulmonale

Scanned with CamScanner

APPROACH TO BLOOD IN SPUTUM (Due to Pulmonary TB)

P/C

1). Blood in sputum or
Cough (productive) for 2months

Patient may present with any of the above complaints but I will proceed with the first one (for cough approach plz see scheme for productive cough in ILD section).

P/C

blood in sputum...

HOPI

My patient who has positive contact Hx with TB patient presented with blood in sputum (do not use medical terminology during HX presentation) for the last.....duration. It is episodic in nature, there are 4-6 episodes per day, and each episode containing 1-2 spoon of blood that is bright red and sometime are in clotted form however, there is no history of bleeding from any other orifice and easy bruising

Now apply ODPARAV

Association (associated features)

- cough (dry or sputum production)
- SOB & wheezy chest sounds
- unintentional weight loss , decreased appetite and fever
- lumps& bumps
- Chest pain and palpitation.

Now exclude important DDS of hemoptysis

- **CA lung**→ there is no Hx of change in the quality of voice, difficulty in swallowing and lumps and bumps
- **Bronchiectasis** →There is no HX of passage copious amount of foul –smelling sputum particularly in the morning with postural drainage
- **ABPA**→No Hx of chronic whistling sound in breathing, chronic use of inhaler or chronic Hx of SOB not responding to any medications
- **Vasculitis like Wagner, microscopic polyngitis, good pasture etc.**→ No Hx of palpable skin rash, blood in urine and arthritis or arthralgia
- **SLE induced alveolar haemorrhage** →No Hx of oral ulcer, photosensitivity, hair fall and arthralgia autoimmune
- **Lung abscess** →No Hx of IV drug abuse, immunosuppressive medication, aspiration of oral contents, poor oral hygiene and alcoholism
- **Coagulopathy**→ Denied family HX of any bleeding disorder or HX of blood thinning medication
- **Necrotizing pneumonia**→, Denied Hx of high-grade fever associated with rigors and chills
- **Pulmonary embolism** →No Hx of prolong immobilization, recent air travel or surgery and

Scanned with CamScanner

unilateral swelling of lower limb (

- **HIV** → No Hx of high-risk sexual behaviour, unscreened blood transfusion and IV drug ab
- **CKD** →No HX of decreased urine output, periorbital swelling, sallow complexion of skin
- **CLD** →No Hx of abdominal distension, blood in vomiting, tarry stool and past HX of HBV HCV infection
- **Valvular heart diseases e.g. Ortner syndrome**→ No Hx of left side chest pain, palpitatic monthly use of intramuscular injection difficulty in swallowing or change in the quality voice

However, there is positive HX of contact with TB patient months/years back

You must ask questions to look for disseminated tuberculosis(TBM , spinal , abdominal etc beside pulmonary TB

Most common causes of blood in sputum in exam are TB, CA lung, bronchiectasis, ABPA and vasculitis.

CARE OF TB

As I told earlier that my patient has positive contact Hx with TB patient … Months/years back but there is no Hx of working in factory, mines, prolong intake of immunosuppressive therapy , HIV and other pre-morbids that prone him to TB and sand blast.

Complication of TB

- **TBM**

My patient denied any HX of altered sensorium, headache, fits or weakness of any part of body.

- **Pot disease**

No Hx of backache, and weakness of lower limb

- **Abdominal TB**

HX of chronic diarrhea that is foul smelling and not responding to treatment (MIXED diarrhea)

- **Lupus vulgaris**

Hx of skin rash or non-healing wound on face

- **Tuberculous pericarditis**

Hx of chest pain on lying flat that improves with leaning forward

- **Renal TB (genitourinary TB)**

Hx of persistent sterile pyuria and ulcer on genetalia

- **Pleural effusion**

Aspiration of fluid from chest cavity

- **Lymphadenopathy**

Hx of swelling of or lumps in neck, axillary and groin region and Hx of discharge from those lumps

- **Ascites and Hepatosplenomegaly**

Hx of abdominal distension and heaviness of right or left hypochondrium

- **Anemia of Chronic Disease**

Scanned with CamScanner

Hx of easy fatigability and pallor of complexion

- **PID**

Hx of pelvic discharge and irregular cycle

- **Addison disease**

Hx of darkening of skin and dizziness on standing

In addition, ask about common complication of treatment like Hx of Acute hepatitis, gout, visual acuity, tingling sensation or paresthesia and orange discoloration of urine

Now ask about ITP

ASK about relevant investigations like sputum for AFB, ESR, and CXR etc. (see viva section Treatment (how many tabs and any side effects) and procedure like bronchoscopy or pleural tap. Ask about relevant **PAMHUG-FOSS-TV-F** (family Hx for contacts or active diseases, socio-economic Hx for source of income and any overcrowding in house and ask about well-ventilated rooms)

EXAMINATION SCHEME

Vitals (checking orthostatic hypotension is compulsory)→**GPE** built ,clubbing , blackening of skin creases, lymphadenopathy, jaundice(ATT induced) ,skin rash, pitting edema and signs of malabsorption) → **RES**P (back of the chest including spinal tenderness & deformity than front of the chest) **CVS** (3rd heart sound, pericarditis, raised JVP as result of constrictive pericarditis and look for lower limb edema)→**abdomen** (Doughy ,ascites, hepatosplenomegaly and mass in RIF)→ CNS (motor+ sensory , cranial nerves ,headache and seizure, spinal tenderness and gibbus deformity if missed in resp system and then cerebellar followed by fundus examination .

Based on HX and clinical examination, my clinical diagnosis is

- Pulmonary TB
- CA-lung

Scanned with CamScanner

VIVA OF TUBERCULOSIS

What are the types of mycobacteria?

A) Mycobacterium tuberculosis complex

It includes M. tuberculosis, M. africanum and M.bovis including others .All can cause tuberculosis

B) Non-Tuberculous mycobacteria

It is further divided into two groups.

Rapidly growing mycobacteria

That includes m.fortuitum group, m.abscessus group, m.chelani, m.mucogenicum etc.

Slow growing mycobacteria

Mycobacterium avium complex (MAC), m.kansasii, m.marinum, m.xenopi etc

C) M.leprae (that causes leprosy also called Hansen's disease)

Group B and C are also called atypical mycobacteria

What is Ghon [illegible]?

Primary alveolar lesion is called Ghon focus that is made by < 10 microgram droplets. It is characteristically situated in the periphery of the lung and estimated lifetime risk after the primary infection is 10%.

What is Ghon Complex?

Combination of the primary complex and regional lymph nodes is called Ghon complex.

What are the risk factors?

All immunocompromised conditions like HIV (↑ risk40%), DM (↑5%) CKD, silicosis, malignancy, steroid and other immunosuppressive drugs, vit D deficiency and gastrointestinal diseases with malabsorption. Other risk factors includes extreme of age, close contact with smear positive and overcrowding

One untreated smear positive patient can transmit TB to 10-15 contacts person in a year.

What is pulmonary, extra pulmonary, miliary and disseminated TB?

Pulmonary TB involves only lung parenchyma

Extra –pulmonary TB (20% in HIV negative population) involves other than lung parenchyma like lung pleura, lymph nodes, CNS, GI tract and joint & bones.

Miliary TB refer to the classical appearance on chest x-ray of 1-2 mm lesion (Millet seeds) distributed throughout the lung fields. It occours due blood-borne dissemination so it could be pulmonary as well as extra pulmonary

Untreated miliary TB carries 100% mortality while treated 10%

Cryptic tuberculosis is an unusual presentation of miliary TB sometimes seen in old age that is characterized by weight loss , intermittent-low grade pyrexia of unknown origin, normal chest x-ray , negative tuberculin-skin test , leukemiod reaction or pancytopenia , hepatosplenomegaly (25-50%). it is confirmed by biopsy with granulomas and /or acid-fast bacilli in liver and bone marrow .

Disseminated TB is when ≥ 2 organs are involved.

Scanned with CamScanner

BCG-vaccine and how much it is protective against TB?

It is live-attenuated vaccine and is 40-70% protective against TB only for 10-15 years.

What are the indications of steroid therapy in TB?

TBM, pericarditis, adrenalitis, miliary TB, bone TB and epididymitis

What do you know about drug resistance?

Classification of tuberculosis based on drug resistance

Mono-resistance

Resistance to one first-line anti TB drug only

Poly-resistance

Resistance to more than one first-line antiTB drugs other than both isoniazid and rifampicin together

Drug resistance TB

Resistance to one first-line antiTB drug either isoniazid or rifampicin

Multi-drug resistance (MDR)

Resistance to isoniazid and rifampicin and possibly additional agents

Extensive drug resistance (XDR)

Resistance to isoniazid, rifampicin, fluoroquinolones and either aminoglycosides or capreomycin or both

Rifampicin resistance (RR)

Resistance to rifampicin detected using phenotypic or genotypic methods, with or without resistance to other anti-TB drugs .it includes any resistance to rifampicin, in the form of mono-resistance, poly resistance, MDR or XDR.

What is latent tuberculosis?

In latent tuberculosis, there is no sign& symptoms and chest –xary is normal .however, there is positive PPD skin test, **interferon gamma release assays** (including QUANtiFERON and T-SPOT tests).Patient with latent tuberculosis cannot transmit the diseases to others. However, reactivation of the diseases may occur if the patient's immune defense is impaired. Active TB may develop in 5-10% of individual with latent TB, half of these occours in the 2 years flowing primary infection

How will you investigate this patient?

- **1st Sputum for AFB light microscopy** (3 morning specimens recommended .combined sensitivity is 70% e.g. 54% 1st, 11% for the 2nd and 5% for the 3rd specimen while early morning specimen increased yield by 12% compared to spot specimen.

How to interpret the result

- 0-9/100 oil immersion field →negative for AFB
- 10-99/ 100 oil immersion field → 1+
- 1-10/single oil immersion field 2+
- >10/ single oil immersion field 3+

Advantages, report available in one day, easily available and cost-effective.

Scanned with CamScanner

Limitation of AFB it cannot differentiate b/w Tuberculous and non-Tuberculous mycobacteria and dead from live mycobacteria.

4-steps of ZN staining are carbolic fuchsin→ heat & rinse → cover the slides with sulfuric acid & rinse →counterstain with 0.3% methylene blue if pink (due to mycolic acid) mycobacteria positive while purple is negative.

ZN (acid-fast) staining of sputum smear alone has sensitivity and negative predicative value that are low (50-80%) with a single smear but may improve to (90%) with serial sampling

2nd Fluorescein microscopy, it is superior to light microscopy

3rd light emitting diode (LED) Fluorescein **microscopy,**

4th AFB culture (gold standard), culture can detect 10-100 bacteria

in Pakistan only solid medium (Lewis Johnson, LJ)are available and result takes 3-4 (or 4-6 Davidson 23rd edition)weeks ,it sensitivity is 76% while liquid medium report takes 10-14 days and having sensitivity of 90% while specificity exceeds 99% for all methods .

5th first line drug susceptibility testing (Liquid medium)

Result takes 1-2 weeks and it is gold standard that should be performing routinely on initial isolate.

6th Gene expert PCR takes < 2 hours, it not only detect TB but also detect rifampicin resistance. It sensitivity and specificity is > 95%

7th Line probe assay for identification of M tuberculosis complex (not available in Pakistan) also called high-performance liquid chromatography .May be useful in areas of low M tuberculosis incidence where nontuberculous mycobacteria are commonly isolated

8th Nucleic acid amplification test, detection (NAAT.TB) sensitivity/specificity high for smear positive specimen (85-96%) while low for smear-negative specimen (66%).

8th Nucleic acid amplification test, resistance marker (NAAT-R)
Multiple assay for rifampicin and isoniazid are available, specificity is >98% while sensitivity varies from 84-96%.

9th Radiological investigations like
Chest- x-ray (cavity or consolidation), CT chest with contrast and MRI brain
What are the invasive investigations?

Pleural fluid analysis, Bronchoscopy with BAL and Transbronchial biopsy, FNAC (of lymph nodes), fasting gastric fluid aspiration

Scanned with CamScanner

What are the recently introduced investigations for tuberculosis?

A. Adenosine deaminase (ADA)

Pleural fluid adenosine deaminase approximately 90% sensitivity and specificity for pleural tuberculosis at level > 70units/L. there are ADA1 and ADA2 isomer .ADA1 < .42 is suggestive of tuberculosis while > 0.42 may signify cancer and empyema

False positive ADA level may occur in empyema, autoimmune disorder and lymphoma.

Pleural fluid IGRA is superior to pleural fluid ADA level. Pleural fluid culture is positive in 23-58% of the cases pleural tuberculosis.

B. Lateral flow urinary lippoarabinomannan assay (LF-LAM)

In smear negative patient (sputum is negative but culture is positive of mycobacterium tuberculosis) and severely ill HIV patients urinary LF-LAM may be useful.

Definitions

a) **Presumptive Tuberculosis:** Any person who presents with symptoms or signs suggestive of tuberculosis (previously known as TB suspect). The most common symptom of pulmonary TB is a productive cough for more than 2 weeks, which may be accompanied by other respiratory symptoms (shortness of breath, chest pains, hemoptysis) and/or constitutional symptoms (loss of appetite, weight loss, fever, night sweats, and fatigue).

b) **Case of tuberculosis:** A definition case of TB or one in which a health worker (clinician or other medical practitioner) has diagnosed TB and had decided to treat the patient with a full course of anti-TB treatment.

Any person given treatment for "TB" should be "recorded as" a case. "Trial" for "TB" treatment should not "be considered as" a method for diagnosis.

c) **Bacteriologically confirmed TB Case:** is one whom a biological specimen is positive by smear microscopy, culture or by a newer method such as Xpert MTB/RIF assays (GeneXpert) or molecular line probe assay. All such cases should be notified, regardless of whether TB treatment has started.

d) **Clinically diagnosed TB case:** is one who does not fulfil the criteria for bacteriological confirmation but has been diagnosed with active TB by a clinician or other medical practitioner who has decided to give the patient a full x-ray abnormalities or suggestive histology and extra pulmonary cases without laboratory confirmation.

Clinically diagnosed cases subsequently found to be bacteriologically positive (before or after starting treatment) should be reclassified as bacteriologically confirmed.

Bacteriologically confirmed or clinically diagnosed cases of TB are also classified according to

- Anatomical site of disease
- History of previous treatment
- Drug resistance
- HIV status

Classification based on anatomical site of disease

- **Pulmonary tuberculosis (PTB)**

Scanned with CamScanner

TB involving the lung parenchyma or the tracheobronchial tree

- **Exrapulmonary Tuberculosis (EPTB)**
  TB involving organs other than the lungs e.g. pleural , lymph nodes, abdomen ,skin, joint , bones , CNS and genitourinary system.
- **Miliary TB**

A patient with both pulmonary and exrapulmonary TB should be classified as case of PTB. That is why miliary TB is classified, as pulmonary TB because there are lesions in the lung .Tuberculous intra-thoracic effusion, without radiographic abnormalities in the lungs constitutes a case of exrapulmonary TB.

Classification based on history of previous TB treatment

- **New patients:** who have never been treated for TB or have taken anti-TB drugs for less than 1 month.
- **Previously treated patients:** who have received 1 month or more or more of anti-TB drugs in the past. They are further classified by the outcome of their most recent course of treatment.
- **Relapse patients:** who have previously been treated for TB, were declared cured or treatment completed at the end of their most recent course of treatment and are now diagnosed with a recurrent episode of TB (either a true relapse or a new episode of TB caused by reinfection)
- **Treatment after** [illegible] **patients:** are those who have previously been treated for TB and whose treatment failed at the end of their most recent course of treatment.
- **Treatment after loss to follow-up patients:** have previously been treated for TB and were declared lost to follow-up at the end of their most recent course of treatment. (These were previously known as treatment after default patients.)
- **Other previously treated patients:** are those who have previously been treated for TB but whose outcome after their most recent course of treatment is unknown or undocumented.
- **Patients with unknown previous TB treatment history:** do not fit into any of the categories listed above.

Classification based on HIV status:

- **HIV-positive TB patient:** refers to any bacteriologically confirmed or clinically diagnosed case of TB who has a positive result from HIV testing conducted at the time of TB diagnosis or other documented evidence of enrolment in HIV care, such as enrolment in the pre-art register in the ART register once ART has been started.
- **HIV-negative TB patient**: refers to any bacteriologically confirmed or clinically diagnosed case of TB who has a negative result from HIV testing conducted at the time of TB diagnosis. Any HIV-negative TB patient subsequently found to be HIV positive should be reclassified accordingly.
- **HIV- status unknown TB patient:** refers to any bacteriologically confirmed or clinically diagnosed case of TB who has no result of HIV care. If the patient's HIV status is subsequently determined, he or she should be reclassified accordingly.

Scanned with CamScanner

Treatment outcome definitions

Make a clear distinction between two types of patients

- patients treated for drug-susceptible TB
- Patients treated for drug-resistant TB using second-line treatment outcome for TB patients (excluding patients treated for RR-TB or MDR-TB) all bacteriologically confirmed and clinically diagnosed TB cases should be assigned an outcome from this list except those with RR-TB or MDR-TB, who are placed on a second line drug regimen.

Outcome	Definition
Cured	A pulmonary TB patient with bacteriologically confirmed TB at the beginning of treatment who was smear-or culture-negative in the last month of treatment and on at least one previous occasion.
Treatment completed	A TB patient who completed treatment either without evidence of failure but with no record to show that sputum smear or culture were negative, because test were not done or because results are unavailable.
Treatment failed	A TB patient whose sputum smear or culture is positive at month 5 or later during treatment.
Died	A TB patient who die for any reason before starting or during treatment.
Loss of follow up	A TB patient who did not start treatment or whose treatment was interrupted for 2 consecutive months or more.
Not evaluated	A TB patient for no treatment outcome is assigned. This includes cases "transferred out" to another treatment unit as well as cases for which the treatment outcome is unknown to reporting unit.
Treatment success	The sum of cured and treatment completed

How would you treat this patient?

- HRZE× 2 months followed by HR for 4months(in case of pyrazinamide resistance than HRE) and vit B6 for entire duration. 6months therapy is appropriate for all patients with new-onset pulmonary TB and most cases of extra pulmonary TB .However 12-months therapy is indicated for meningeal , spinal ,and bone TB(2months HRZE and 10 months HR).where drug resistance is not anticipated , patients can be assumed to be non-infectious after 2weeks of therapy .

How would you monitor the response?

Effectiveness of therapy is assessed by further sputum smear at the end of 2months, start of 5months and at the end of th6th months and By weight gain (and not by chest-x-ray)

When you will label patient as treatment failure?

If patient is still smear positive at the start of 5month than this is treatment failure. Do Xpert/MTB, Rif assay and send culture and sensitivity. If RR is not detected then restart ATT as RE treatment case and if RR detected than refer to management of DR TB

How would you Re-treat a Patient?

Scanned with CamScanner

All smear positive cases identified as "failure " treatment after lost to follow-up and relapses cases are candidates for Re-treatment .

Before embarking on treatment, drug –susceptibility testing should be conducted after registration for Re-treatment .therefore, all cases eligible for re-treatment will be tested for rifampicin (GeneXpert) and isoniazid resistance status.

What is the Re-treatment Regimen?

Intensive phase

3HRZE e.g. all the 4 medicine for 3months

Continuation phase

5HRE e.g. 3 medicine for 5months

How will you check the effectiveness of treatment?

Clinically by improvement of symptoms and weight-gain and performing sputum examination at the end of 3rd, 5th and 8th months

What is re-treatment failure and how would you manage this case

When patient is still sputum positive at the end of the 5th month or a case of relapse while having completed the full course of re-treatment regimen

Management

This particular group is considered drug-resistant TB (DR-TB) and their sputum should be collected for culture and sensitivity before the start of their treatment.

All patients have to be referred to DR TB center for management where they will design special treatment regimen that involve combination of 2nd line antiTB drug based on the bacteriological (Culture and sensitivity)result.

Key-subgroups

i. **Renal failure and severe renal insufficiency**

Isoniazid and rifampicin are execrated by biliary route and does not need dose adjustment while pyrazinamide and ethambutol are eliminated via renal route and needs dose adjustment in CKD stage iii and onward so these two drugs should be given on alternate days (3times/week) at the recommended doses e.g. pyrazinamide 25mg/kg and ethambutol 15mg/kg.Streptomycin should be avoided due to ↑risk of nephrotoxicity and ototoxicity .if streptomycin must be used, the recommended dose is 15mg/kg, two or three times/week and serum level of the drug should be closely monitored

ii. **Liver disorders**

A.Child-Pugh A

Two hepatotoxic regimens like

Isoniazid, rifampicin and ethambutol for 9 months (HER) (for susceptible bugs) or

2months of isoniazid, rifampicin and ethambutol plus streptomycin followed by isoniazid and rifampicin for 6months (2HERS +6HR)

B.Child-Pugh B

One Hepatotoxic Drug

2 months of streptomycin, isoniazid and ethambutol followed by 10 months of isoniazid and ethambutol (2SHE+10HE)

C.Child-Pugh C

One hepatotoxic drug

Streptomycin, levofloxacin (fluoroquinolones) and ethambutol **(SLE)** for 18 -24months with close monitoring of the liver function parameters.

Scanned with CamScanner

iii. **Pregnancy and location**

1st line ATT is safe during pregnancy and lactation. while according to CMDT2024 , since the risk of teratogenicity with pyrazinamide has not been clearly defined ,pyrazinamide should be used only if resistance to drug is documented and susceptibility to pyrazinamide is likely **and that is why rifampicin ,isoniazid and ethambutol for 2months followed by rifampicin and isoniazid for 7 months** and ethambutol can be stopped after the first months if isoniazid and rifampicin susceptibility is confirmed .pregnant women taking isoniazid should take pyridoxine (vit B_6) 10-25 mg orally once a day, to prevent peripheral neuropathy .

- Rifampicin is enzyme inducer so female on OCP should ↑ the dose of OCP if taking rifampicin containing regimen.

iv. **HIV AND TB**

The basic approach to patients with HIV who have tuberculosis is similar to those patients without HIV. Additional considerations include, longer duration of therapy, drug interaction between rifamycin derivatives such as rifampin and rifabutin used to treat tuberculosis and some of the protease inhibitors and nonnucleoside reverse transcriptase inhibitors (NNRTIs) use to treat HIV .DOT is recommended for all patient with tuberculosis and HIV.

v. **Management of ATT adverse effects**

Here we ll only discuss only ATT induced hepatitis that is frequently asked in exam

A.**Asymptomatic Patients**

ATT should be stopped if ALT is > 5 times normal

B.Symptomatic Patients

In symptomatic patients (vomiting, abdominal pain &tenderness, **right** upper quadrant abdominal pain, jaundice and abnormal LFTs) if LFTs are normal than treat the patient symptomatically but if ALT> 3 times normal ATT should be stooped until baseline ALT get back to baseline(< 2 times of the upper limit of normal) .however ,if ATT cannot be hold due to patient ,s serious clinical condition including TBM , pericardial disease and Potts disease than various regimen are available to continue ATT like streptomycin, ethambutol and levofloxacin (fluoroquinolones) e.g. (SLE) till improvement of adverse reaction .

ATT Re-Challenge Protocol

- Re-challenge the patient once symptoms improves and ALT get back to normal, by adding one by one drug every 4 days, start from low dose and titrate it on 2nd and 3rd day .for example start with rifampicin 75mg on day 1st and if patient tolerate the dose than titrate the dose to 300mg on 2nd day followed by full dose on 3rd and 4th day along with ALT monitoring followed by introduction of isoniazid then pyrazinamide with same protocol.
- If sign and symptoms recur with re-challenge of a particular drug than stop that drug and modify the treatment regimen and/or duration of the therapy as needed.
- There are certain alternative regimens depend on which particular drug is the culprit of drug induced liver injury (DILI).

  - **rifampicin induced liver injury regimen**

    2SHE+ 10 HE

2 months of streptomycin, isoniazid, and ethambutol followed by 10months of isoniazid and ethambutol (no rifampicin).

  - **Isoniazid induced liver injury**

Rifampicin, pyrazinamide and ethambutol for 6-9 months

  - **Pyrazinamide .....**

Scanned with CamScanner

if pyrazinamide is discontinued before the patient has completed the intensive phase, than isoniazid and rifampicin therapy may be extended 9 months.

- **Isoniazid & rifampicin .....**

If both drugs can't be used than non-hepatotoxic regimen consisting of **SLE**
E.g. streptomycin, levofloxacin (fluoroquinolones) and ethambutol should be used for 18-24months.

Prognosis of TB

Tuberculosis is often a deadly disease without treatment. 5 years prognosis without treatment, the outcome of smear –positive pulmonary TB (PTB) in HIV negative patients is as follow

- 50-60% die
- 20-25% are cured spontaneously
- 20-25% develop chronic smear –positive TB.

- more than 20% of global TB-related burden may be attributed to smoking and it signify a strong relationship between smoking and TB

However, if the right drugs are taken for the right duration, tuberculosis is curable > 95%.

Managing contact of TB

- Contacts are the people who have been sharing the same living premises and the daily life activities with the patients.
- Adults and children > 5yrs with sign and symptoms suggestive of tuberculosis (cough> 2 weeks, weight loss, fever,) should be counselled to visit TB care center for screening for TB along with the close contacts and household members.
- while all children < 5yrs who are not suffering from any symptoms are put on isoniazid 5mg/kg prophylaxis for 6months
- Child who is breast-fed by sputum smear –positive mother would continue breast feed and should be prescribed isoniazid 5mg/kg for 6months and then BCG vaccine.

Scanned with CamScanner

Regimen options and factors to be considered for selection of treatment regimens for patients with MDR/RR-TB

Regimen	MDR/RR-TB fluoroquinolones susceptible	Pre-XDR-TB	XDR-TB	Extensive pulmonary TB	Exrapulmonary TB	Age <14year
6-month BPaLM/BpaL	Yes (BPaLM)	Yes (BpaL)	NO	YES	Yes-except TB involving, CNS, miliary TB and osteoarticular TB	NO
9-Month all-oral	YES	Yes	No	No	Yes-except TB meningitis miliary TB, Osteoarticular TB and pericardial TB	YES
Longer individualized 18-month	Yes/No	Yes/No	Yes	Yes	Yes	YES
Additional factors to be considered if several regimen are possible	Drug intolerance or adverse events					
	Treatment history, previous exposure to regimen component drugs or like hood of drug effectiveness					
	Patient or family preference					
	Access to and cost of regimen component drugs					

MDR –TB

MDR-TB is caused my mycobacterium tuberculosis strain that are resistant to at least both rifampicin and isoniazid

Rifampicin –resistant TB caused by strain resistant to rifampicin and these strains may be susceptible or resistant to isoniazid(MDR-TB) or resistant to other first-line or second line TB medicine .MDR and RRTB are often grouped together as MDR/RR-TB and are candidates for treatment with MDR-TB regimens.

MDR TB regimens (2022 WHO updates)

1) **BPaLM or BPaL regimen**

Eligibility

- All pulmonary TB or extra pulmonary TB except TBM, disseminated(miliary TB) and osteoarticular TB
- age≥ 14 years
- no-known allergy to regimen component drugs
- no evidence of resistance to any drugs or patient has not been previously exposed to any of the component drugs for 4 weeks or longer and if so but no evidence of resistance to any specific drugs with such exposure has been definitely been rule-out .
- no XDR-TB according to 2021 WHO definition
- patient is not pregnant or breastfeeding

Scanned with CamScanner

- **Dosing of component drugs for adult and adolescent (aged≥14years)**
- Bedaqulin(100mg) 400mg once daily for 2 weeks , then 200mg 3times /week afterward or 200mg daily for 8 weeks , then 100mg daily
- pretomanid (200mg tablet) , 200mg once daily
- linèzolid (600mg tablet) 600mg once daily
- moxifloxacin(400mg tablet) 400mg once daily

BPAL regimen

BPAL regimen can be prescribed for those that have proven fluoroquinolones resistance but if there is suspected resistance than use BPaLM regimen and exclude moxifloxacin once resistance is confirmed.

Duration of treatment

- Patient with susceptibility to fluoroquinolones cab be started on the BPaLM regimen for 6months (26weeks). In the case of fluoroquinolones resistance, identified after treatment initiation, moxifloxacin may be discontinued and the regimen can be continued as BPaL.
- individuals who switch from BPaLM to BpaL should consider their treatment date the same as the date for BPaLM
- When the regimen is BpaL from the start of the therapy or is changed to BpaL, it can be extended to 9 months (39weeks).
- Linezolid is by far the most toxic drug in the regimen and therefore require significant monitoring and at times mitigation strategy to reduce adverse effect. Linezolid should be continue at the full dose for the entire duration, the dose of linezolid can be reduced to 300mg or discontinued (and restarted when possible) if there is significant toxicity. in general, action should be taken in the following manner for the common toxicities associated with linezolid:
- for optic neuritis diagnosed at any grade, permanent discontinuation of linezolid is indicated;
- for peripheral neuropathy grade-2, reduce the dose of linezolid to 300 mg per day with a possible drug holiday for 1-2 weak before dose reduction;
- for peripheral neuropathy grade 3 or 4, in most cases permanent suspension of linezolid well be needed; in some cases , after a 1-2 weak drug holiday and reversion to grade 2, the linezolid can be restarted and tolerated, provided at does not revert back to a grade 3 or 4(caution is warranted with this approach because patients can be left with sever painful and disabling permanent peripheral neuropathy); and
- Myelosuppression (even of grade 3 or 4) is often reversible with a short 1-to-2 week drug holiday followed by reducing the dos of linezolid to 300 mg per day; severe anemia may need to be treated with transfusions or erythropoietin.

2 .the 9-month all-oral regimen for multidrug –resistance or rifampicin resistant tuberculosis MDR /RR TB (Shorter regimen 9-12months)

WHO (2022 recommendation) suggest the use of the 9-months all –oral regimen rather than longer regimens (18-months) in patients with MDR/RR-TB and in whom resistance to fluoroquinolones has been excluded.

the 9-months all-oral regimens consist of bedaquiline(used for 6months), in combination with levofloxacin /moxifloxacin , ethionamide, ethambutol, isoniazid (high dose) ,pyrazinamide and clofazimine(for 4 months with the possibility of extending to 6-months if the patient remain sputum smear positive at the end of 4-months) followed by treatment with

Scanned with CamScanner

levofloxacin/moxifloxacin ,clofazimine ,ethambutol and pyrazinamide for 5-months . Ethionamide can be replaced by 2months of linezolid (600mg) daily.

i. Ethionamide variation

Initial phase: 4-6 $Bdq_{(6m)}$-Lfx/Mfx-Cfz-Z-E-Hh-Eto (7 drugs)

Ethionamide and high dose isoniazid are dropped after 4 or 6months depending on sputum smear status

Continuation phase: 5 Lfx/Mfx-Cfz-Z-E

Bedaquiline is usually given for 6months but could be extended ton 9-months, particularly if the initial phase is extended from 4 to 6 months due to a lack of sputum conversion at 4months

ii. linezolid variation

Initial phase: 4-6 $Bdq_{(6m)}$- $Lzd_{(2m)}$-Lfx/Mfx-Cfz-Z-E-Hh-

Continuation phase: 5 Lfx/Mfx-Cfz-Z-E

Eligibility

- 9-months all-oral regimen (with either ethionamide or linezolid) may be offered with MDR/RR-TB (where resistance to at least rifampicin has been confirmed and resistance to fluoroquinolones has been ruled out)
- no documented resistance or suspected ineffectiveness of bedaquiline ,clofazimine ,or ethionamide or linezolid
- exposure to previous treatment of same regimen drugs (2^{nd} line) for no more than 1 months
- women who are pregnant or breastfeeding ,these patient may be considered eligible for the linezolid –containing 9-months regimen, but should not receive 9-months ethionamide regimen
- all people living with or without HIV
- Those with no extensive (presence of BL cavitary disease or extensive parenchymal involvement) or severe TB disease and no severe & complicated extra- pulmonary TB (. pericardial and osteoarticular MDR/TT-TB patient are not eligible for short-term regimen but for longer regimen).

Patient subgroup

a. **patient with hepatic dysfunction**

this 9-months regimen may not be the most appropriate option for people with chronic liver disease because it contain several potentially hepatotoxic drugs like pyrazinamide, isoniazid and ethionamide .Although, this regimen may still be offered with closed monitoring of liver enzyme in people with chronic stable liver dysfunction, however a longer regimen with fewer hepatotoxic drugs may be preferable in setting where closer monitoring is not feasible

b. **patient with renal failure**

this9-months regimen may be used to treat MDR/RR-TB in patient with renal failure provided the dose or dosing interval of renally excreted drug are adjusted for the patient creatinine clearance .levofloxacin (but not moxifloxacin) ethambutol and pyrazinamide require dose or frequency adjustment for adults with creatinine clearance less than 30ml/mint treatment does not to be extended unless indicated by lack of sputum smear conversion at 4months, as for patients with normal renal function

3. THE LONGER REGIMENS

In MDR/RR-TB patient on longer regimens all three group A agents and at least one group B agent should be included to ensure that treatment start with at-least 4 TB agents likely to be effective , and that at-least 3 agents are included for the rest of treatment if bedaquiline is stopped .if only one or two group A agents are used ,both group B agents are to be included .if the

Scanned with CamScanner

regimens cannot be composed with agents from group A and B alone, Group C agents are added to complete it.

Eligibility

A Longer treatment regimen should be proposed mainly when the BPaLM/ BpaL or 9-month all-oral regimen cannot be used.

A longer regimen is expected to be used in the following situation.

- severe exrapulmonary TB;
- additional resistance to key medicines of the BPaLM/BpaL regimen (except moxifloxacin)are the 9-month all-oral regimen;
- lack of response to shorter treatment regimens (e.g. treatment failure due to no bacteriological conversion, no clinical response , emerging residents or loss to follow-up)
- drugs intolerance to the component medicine of the BPaLM /BpaL regimens (except moxifloxacin or 9-months shorter all-oral treatment regimen ; and
- pregnant and lactating women who could not benefit from the 9-months shorter regimen owing to certain clinical condition or children aged below 14-year who could not be treated with BPaLM/BpaL or who , for any reason , cannot opt for a 9-month regimen

Grouping of medicines recommended for use in longer MDR-TB regimens.

Group and steps	Medicine and	abbreviation
Group A Include all three	Levofloxacin or	Lfx
	Moxifloxacin	Mfx
Medicines	Bedaquiline	bqd
	Linezolid	Lzd
Group B Add one or both medicine	Clofazimine	Cfz
	Cycloserine or	Cs
	Terizidone	trd
	Ethambutol	E
	Delamanid	Dlm
	pyrazinamide	Z
Group C: Add to complete the regimen, and when medicines from Group A and B cannot be used Ipm-Cln	Imipenem-cilastin or meropenem	Mpm
	Streptomycinh	s
	Ethionamide or Prothionomide	Eto
	P-aminosalicylic acid	PAS

- Kanamycin, capreomycin and clavulanic acid should not be used in the treatment of MDR/RR-TB patient on longer regimen.
- levofloxacin or moxifloxacin should be included in MDR/RR-TB patients on longer regimen

Scanned with CamScanner

- **Bedaquiline** should be included in longer regimen for MDR-TB patient > 6 years (children<6yr with MDR/RR-TB , an all-oral treatment regimen containing bedaquiline may be sued)
- Linezolid, clofazimine & cycloserine or terizidone, ethambutol, Delamanid, pyrazinamide, Imipenem-cilastatin, Amikacin (≥18 years with close monitoring for adverse effects if Amikacin is not available, streptomycin may replace under the same condition).
- **Ethionamide or prothionomidei** and **p-aminosalicylic acid** may be included in the treatment of MDR/RR-TB patients on longer regimen only if bedaquiline, linezolid, clofazimine or delaminde are not used, or if better option to compose regimen are not possible.

At least four drugs must be selected, starting from group A and then group B. group C drugs are usually included in longer regimen if it cannot be composed with group A and B alone.

Duration of the regimen

in MDR/RR-TB patient on longer regimen, a total duration of 18-20months is suggested for most patients .while treatment duration of 15-17 months after culture conversion or in MDR/RR-TB patient on longer regimen containing Amikacin or streptomycin, **an intensive phase of 6-7 months** is suggested for most patient; the duration may be modified according to the patients response to therapy.

- 18-20 months was determined to be an optimal duration to maximize treatment success

Key –Subgroups

1) HIV

Currently, there are no specific changes in using longer regimen in HIV. However, there can be cumulative risk factors for clinical complications, toxicities and drug-drug interaction.

2) pregnant and lactating women

dosing and safety data to support the optimal use of second-line TB medicine during pregnancy are generally spare .even less is known about the effect of MDR/RR-TB treatment on the infant in-utero and after birth .however, in general, the benefits (to both parent and child) of providing effective MDR/RR-TB treatment to parent far outweigh the potential risks posed to the fetus in-utero or the breastfed infant.

- ethionamide is contraindicated in pregnancy

3) DR-TB in patients with hepatitis B or C

There are limited data on the use of longer treatment regimen among people with viral hepatitis, or undergoing treatment for hepatitis C, It may be prudent to monitor closely for drug-drug interaction and hepatotoxicity among this patient group.

Monitoring treatment response and outcome assignment

Response to the treatment is monitored on the basis of monthly sputum smear microscopy, as well as culture, ideally at the same frequency. Monthly culture

Increased the detection patients with a true positive bacteriological result when compared with sputum smear microscopy alone; also, it reduced the proportion of patients with false negative result.

Concomitant use of sputum smear microscopy and culture test results help to identify patients whose bacteriology remains positive or revert to positive following initial conversion to negative.

Scanned with CamScanner

This combined testing will help clinicians to identify patients whose treatment is likely to fail, and thus to plan alternative options and institute infection control measures in timely manner. Additional benefit would be expected from reduced transmission and development of resistance, and from appropriate changes to treatment regimens. Regular microscopy and culture of sputum or other specimens remain important to ensure that treatment failure is detected early. The frequency of these examinations is similar to the schedule used in patients on the 9-month all-oral MDR-TB regimen and the BPaLM/BPaL regimen.

The treatment outcome definitions and reporting framework for patients on longer regimen are the same as those for patients on other MDR-TB regimens (38). The updated definitions of treatment failure include situations where a patient's treatment regimen has been terminated or permanently changed to a new treatment regimen, owing to;

- no clinical or bacteriological response to treatment:
- adverse drug reaction; and
- Evidence of additional drug resistance to medicines in the regimen.

Bacteriological failures are considered when patients treated with a longer regimen remain positive without conversion, or revert to positive following initial conversion to negative.

Failure due to adverse drug reactions or drug resistance is considered when additional resistance emerges while the patient is on a longer regimen, or the regimen needs to be stopped because of a severe adverse event....

Treatment of MDR/RR-TB patients with HIV

ART is recommended for all patients with HIV and drugs –resistant TB requiting second-line anti-tuberculosis drugs irrespective of CD4 cell count, as early as possible (within the first 8 weeks or within first 2 weeks if CD4 is <50 cells/mm^3) following initiation of anti-tuberculosis treatment .it is not recommended to use bedaquiline and efavirinze in combination

What kind of surgery is recommended in the treatment of MDR/RR-TB?

Elective partial lung resection (lobectomy or wedge resection) may be used as an adjunct to combination medical therapy for MDR-TB.

4. Regimen for rifampicin-susceptible and isoniazid –resistant TB (Hr-TB)

Rifampicin, ethambutol, pyrazinamide and levofloxacin are recommended for 6 months.

In patient with confirmed rifampicin-susceptible, isoniazid resistant tuberculosis it is not recommended to add streptomycin or any other injectable to the treatment regimen.

Health education and counselling on the disease and treatment adherence should be provided to the all TB patients.

Scanned with CamScanner

LATENT TUBERCULOSIS

Treatment of latent tuberculosis

(For definition and investigation, see investigations section)

Individuals with latent tuberculosis infection do not have active disease and cannot transmit the organism to others. However, reactivation of disease may occur if patients' immune systems are impaired .Active, tuberculosis will develop in 5-15% of individuals with latent TB who are not given preventive therapy; half of the cases occur in the first 2 years after primary infection.

Treatment is essential to controlling and eliminating tuberculosis and substantially reduces the risk that infection will progress to active disease. In general, patients with a positive tuberculin skin test or interferon gamma release assay who are at increased risk for exposure or disease are treated .it is essential that each person who meets the criteria for treatment of latent tuberculosis infection undergo a careful assessment to **exclude active disease** . Immunosuppressive close contact of person with active tuberculosis should be evaluated for treatment of latent tuberculosis infection despite a negative tuberculin skin test reaction (< 5mm induration). Close contact with negative tuberculin skin test should be retested 10-12 weeks later. There are different treatment regimens available for HIV negative and positive patients.

- **isoniazid**

  A 9-months oral regimen is preferable to 6months of therapy with daily dose of 300mg or twice-weekly 15mg/kg. Those with risk of peripheral neuropathy (DM, CKD, malnutrition, alcoholism, pregnancy etc.) may be given supplemental pyridoxine (vit B_6), 10-15 mg/day.

- **isoniazid & rifampin**

  A 3-months oral regimen of daily isoniazid (300mg) and rifampin (600mg)

- **isoniazid & rifapentine ;**

  A 3-months oral regimen of once weekly isoniazid 15mg/kg and rifapentine 15-30mg/kg

- **Rifampin**

  Patient who cannot tolerate isoniazid can be considered for a 4-months oral regimen of rifampin at 600mg daily.

- **Isoniazid –resistant ,rifampicin sensitive TB close contacts**

  They should receive 2 months therapy of rifampicin and pyrazinamide or a 4-months regimen of daily rifampin alone.

- contacts of persons with drug –resistant tuberculosis should receive two drugs to which the infective organism has demonstrated susceptibility
- Contacts in which the tuberculin skin test or interferon gamma release assay is negative and contacts who are HIV seronegative may be observed without treatment or treated for 6 months.
- HIV-positive contact should be treated for 12 months.
- All contacts of persons with multidrug- resistant tuberculosis or extensively drug-resistant tuberculosis should have 2 years of follow-up regardless of type of treatment.

Scanned with CamScanner

- persons with a positive tuberculin skin test (5mm or more of induration) and fibrotic lesions suggestive of old tuberculosis on chest radiographs who have no evidence of active disease and no history of treatment for tuberculosis should receive 9 months of isoniazid or 4 months of rifampin (with or without isoniazid).pregnant or breast-feeding women with latent tuberculosis should receive either daily or twice isoniazid with pyridoxine (vitamin B6).

Main Adverse Reaction Of Antitubeculous Drugs

	Isoniazid	**Rifampicin**	**Pyrazinamide**	**Streptomycin**	**Ethambutol**	**Bedaquiline**
Mode of action	Cell wall synthesis (Delaminide,pretominide has same mode of action)	DNA Transcription	Unknown	Protein synthesis	Cell wall synthesis	In habit ATP synthesis of Bacteria
major adverse reactions	Peripheral Neuropathy Hepatitis Rash	Febrile reactions Hepatitis Rash Gastrointestinal Disturbance	Hepatitis Gastrointestinal Disturbance Hyperuicaemia	8th nerve damage Rash	Retro bulbar neuritis Arthralgia	
Less common adverse Reactions	Lupoid reactions Seizures Psychoses	Interstitial nephritis Thrombocytopenia Hemolytic anemia	Rash Photosensitization Gout	Nephrotoxicity Agranulocytosis	peripheral neuropathy rash	

What are the indications to stop ATT.?

- deafness due to ATT
- liver failure & severe jaundice
- skin rash, optic neuritis
- AKI ,shock and confusion
- >3 stool/day
- pyrazinamide induced arthritis →**don't stop**

What are the indications of surgery in TB patients?

- Hydrocephalous

Scanned with CamScanner

- pericardial effusion
- massive hemoptysis
- Empyema and /or fistula
- obstructive uropathy
- resistant TB and unilateral lung involvement
- Gibbus deformity

Weight based dose of ATT

- INH→5mg/kg (4-6mg/kg)
- Rifampicin →10mg/kg (8-12mg/kg)
- Ethambutol→15mg/kg(15-25mg/kg)
- pyrazinamide →25mg/kg(20-30mg/kg)

Fixed Dose Combination

- 30-39kg→2 tab of ATT
- 40-54 kg→3 tab…
- 55-70 kg →4tab
- >70kg →5tab

Difference between myrin-p and myrin P forte

- **Myrin-P forte**
  INH→75mg, R→150mg, Z→400mg, E→275mg
- **Myrin-P**
  INH→60mg, R→120mg, Z→300mg, E→225mg
  - DOT→Directly observed therapy
  - VDOT→ Video Directly observed therapy
- **How would you treat NTM?**

Rifampicin, ethambutol and macrolide like for 2years

Spinal TB

- gibbus deformity ≥2 vertebral involvement and kyphosis ≥ 6 vertebrae involved
- diagnosed by MRI , bone biopsy (99.9 % diagnostic accuracy)
- spread by haematogenous and paravertebral venous plexuses

Types of pott,s disease

- Central → single vertebral involvement
- Paradiscal →when two adjacent vertebrae involved and is the most common type
- Anterior , posterior and articular

Treatment

- ATT 9-12 months along with steroid for 1-2 months
- Surgical treatment include decompressive surgery and laminectomy

What are the Recent Advances in TB treatment?

- CDC 4-month regimen for drug-susceptible pulmonary tuberculosis as alternative to 6 months therapy

Scanned with CamScanner

- age≥ 12 years and body weight should be ≥40kg
- pulmonary TB caused by organism that are not known or suspected and no contraindication to this regimen
- it is not indicated in pregnancy ,breastfeeding and extra-pulmonary TB
- it consist of intensive phase of 8 weeks duration followed by continuation phase of 9 weeks

Intensive phase

rifapentine 1200mg, moxifloxacin 400mg ,isoniazid 300mg and pyrazinamide(depends on body weight) 1,000mg for 40-55 daily for 8 weeks(56) doses.

Continuation phase

Same dose except pyrazinamide is excluded, for 9 weeks (63 doses).

Scanned with CamScanner

APPROACH TO WORSENING OF SHORTNESS OF BREATH (Due to Heart Failure)

P/C

i. **Worsening of shortness of breath**
ii. **or pedal edema**

HOPI (and ODPARAV) my patient who is diabetic, hypertensive, smoker (….pack years) and ischemic heart disease presented with worsening of shortness of breath for the last 10 days. SOB was of sudden in onset and progressive in nature .initially, he experienced shortness of breath on moderate-severe exertion like walking upstairs but for the last 4 days, he became shortness of breath on mild exertion like walking on flat ground after…….steps .SOB was aggravated by exertion and relived with rest. Patients also complaining of shortness of breath while lying flat and disturbed night sleep that is relieved by prop-up position by using 2-3 pillows .Shortness of breath is associated with cough , that is productive (1-2tTSF) and mostly at night and episodic palpitation as describe by feeling of racing of the heart. Patients symptoms are exacerbated by exertion, however, it doesn't relived by any medication or other remedy

Now exclude DDs of shortness of breath

- Heart failure (long case)
- **Asthma** →No HX of SOB with dry cough that is worse in the late night & early morning e.g. diurnal variation and associated with wheezy chest sounds
- **COPD**→ No HX of SOB with productive cough that is worse during the winter season and patient is using inhaler
- **Pneumonia**→ There is no HX of high grade fever, rigors and chills with rusty sputum
- **Pulmonary TB**→ There is no of low grade fever, night sweats, weight loss and productive cough that is sometime stain With Blood
- **Bronchiectasis**→ There is no HX of copious amount of foul smelling sputum that is worse during the morning and at certain position
- **ILD**→ There is no Hx of SOB and dry cough and past Hx of exposure to factory, particles, fumes, farm, dusts, drugs & radiation or known case of connective tissue disorder.
- **Pleural effusion** →There is no Hx of collection or drainage of fluid from chest cavity
- **Cor Pulmonale** →There is no Hx of some lung pathology, now presented with lower limbs & abdominal swelling, prominent neck veins and tender right hypochondrium (congestive hepatomegaly)
- **Sarcoidosis** →There is no HX Painful skin lesion on shin
- **CA lung**→ There is no Hx of weight loss, decrease appetite, change in the quality of voice (hoarseness), difficulty in swallowing and lumps and bumps in the body
- ***Connective Tissue Disorders and Vasculitis.***
  A general description →There is no Hx of oral ulcers, photosensitivity, hair fall, arthralgia or arthritis, (palpable) petechial skin rash and blood in sputum or urine plus constitutional symptoms.
- ***Anemia***→ There is no Hx of SOB associated with Change in the complexion, palmar and

Scanned with CamScanner

conjunctival pallor, racing of heartbeats and easy fatigability that is non-fluctuating.

- ***CKD***→ There is no Hx of decrease urine output, blood in the urine or frothy urine and patient is on renal replacement therapy.
- **CLD**→There is no Hx of blood in the vomitus, black tarry fouls smelling stools and abdominal distension yellow discoloration of sclera.
- **Thyroid Disorder (Hypo/Hyper** →There is no Hx of associated with heat intolerance, excessive sweating, and involuntary movements of hands, loose motions and irritability and swelling in the neck and

Hx of cold intolerance, weight gain, periorbital puffiness, sluggish mental activities, dry rough skin and swelling in the neck

- **Neuromuscular Disorder (MG, MND, GBS etc.)** →Hx of fluctuating weakness that is more at the end of the day associated with double vision or regurgitation of foods and difficulty in swallowing.
- **(Recurrent) Thromboembolism**→Hx of prolong embolization, recent travel, family Hx of lower limb swelling (DVT due to hypercoagulable state.
  - **exclude few relevant diagnosis**

2. Approach to Ankle Swelling (Pedal Edema)

Patient presented with ankle swelling that is gradual in onset, one week in duration and progressive in nature involving both feet followed by bilateral thigh, abdominal wall and finally facial involvement.

- ascending pattern → heart failure
- descending pattern →renal failure

there is formation of a pit or/ depression on pressing .this swelling is exacerbated by prolong standing and walking while it is decreased by placing pillow under feet .initially it was relived with diuretics but now it is unresponsive to treatment . Patient experiences heaviness in limbs leads to difficulty in walking; however, there is no Hx of overlying skin changes like redness, itching or pain. this swelling is associated with shortness of breath on mild –moderate exertion , lying flat and disturbed night sleep that improve on prop-up position, although, patient denied any chest pain , yellow sclera and pain in right hypochondrium.

DDs of ankle swelling

- **heart failure (long** case here)
- **constrictive pericarditis** →No Hx of distended neck vein, contact or past HX of TB
- **Cor-Pulmonale** →There is no Hx of chronic lung pathology like COPD, ILD, which are associated with these symptoms
- **Hypoalbuminemia**→ There is no Hx of decreased intake of protein diet, chronic diarrhea
- **Chronic Liver Disease** →There is no Hx of chronic hepatitis B&C infection, black tarry stool and blood in vomiting
- **CKD/Nephrotic syndrome** →There is no Hx of decrease urine output, blood in the urine or frothy urine and patient is on renal replacement therapy.
- **autoimmune disorder** →There is no Hx of oral ulcers, photosensitivity, hair fall, arthralgia or

Scanned with CamScanner

arthritis, (palpable) petechial skin rash and blood in sputum or urine plus constitutional symptoms

- **Cushing syndrome** →There is no Hx of moon face, easy brusibility, new onset diabetes and hypertension
- **Drugs** →there is no Hx of prolong intake of medicine like NSAID, CCB, steroid and anti-diabetic like pioglitazone
- **pelvic radiation ,surgery and trauma**
- **Malignancy** No Hx of weight loss, lumps& bumps, and decreased appetite
- **Remember 6Cs for all sort of body swelling**
  - CCF
  - CKD
  - CLD
  - Cor-Pulmonale
  - Cancer
  - chronic diarrhoea

CARE of Heart Failure

- **DM**

  HX dates back to 15 years ago when patient was diagnosed as diabetic (on routine investigation) and started on oral anti-diabetic medication along with dietary advice to which patient was poorly complaint. During the following years, patient treatment was modified many times and for the last, …year's patient is on insulin and taking …Units of insulin (in morning and evening, describe the regimen) .however, patient denied, any Hx of weakness of any part of the body, numbness of feet, frothy urine, blurring of vision or any foot ulcer and Hx of sweating, tremors and loss of consciousness (low blood glucose level)

- **HTN**

  HX dates back 10 years ago, when patient presented to a local hospital with headache and subsequently diagnosed as hypertensive and prescribed anti-hypertensive medicine to which he was not –complaint .however, patient denied Hx of emergency visit or admitted for high blood pressure(described complication if any)

- **IHD**

1 year back patient was admitted in a tertiary care hospital due to central chest pain, sweating and apprehension where he was informed that he had myocardial infarction and thrombolysed .he was discharged with routine cardiac medication and advice of angiography that he did follow. However, he is complaint to cardiac medication.

- **Valvular heart diseases**

Like degenerative aortic stenosis and mitral & aortic regurgitation

- **Arrhythmias like atrial fibrillation with rapid ventricular response**

No Hx of palpitation, abnormal heartbeat and dizziness

- **Smoking**

Scanned with CamScanner

arthritis, (palpable) petechial skin rash and blood in sputum or urine plus constitutional symptoms

Cushing syndrome →There is no Hx of moon face, easy brusibility, new onset diabetes and hypertension

Drugs →there is no Hx of prolong intake of medicine like NSAID, CCB, steroid and anti-diabetic like pioglitazone

pelvic radiation ,surgery and trauma

Malignancy No Hx of weight loss, lumps& bumps, and decreased appetite

Remember 6Cs for all sort of body swelling

- CCF
- CKD
- CLD
- Cor-Pulmonale
- Cancer
- chronic diarrhoea

ARE of Heart Failure

- **DM**

HX dates back to 15 years ago when patient was diagnosed as diabetic (on routine investigation) and started on oral anti-diabetic medication along with dietary advice to which patient was poorly complaint. During the following years, patient treatment was modified many times and for the last, …year's patient is on insulin and taking …Units of insulin (in morning and evening, describe the regimen) .however, patient denied, any Hx of weakness of any part of the body, numbness of feet, frothy urine, blurring of vision or any foot ulcer and Hx of sweating, tremors and loss of consciousness (low blood glucose level)

- **HTN**

HX dates back 10 years ago, when patient presented to a local hospital with headache and subsequently diagnosed as hypertensive and prescribed anti-hypertensive medicine to which he was not –complaint .however, patient denied Hx of emergency visit or admitted for high blood pressure(described complication if any)

- **IHD**

1 year back patient was admitted in a tertiary care hospital due to central chest pain, sweating and apprehension where he was informed that he had myocardial infarction and thrombolysed .he was discharged with routine cardiac medication and advice of angiography that he did follow. However, he is complaint to cardiac medication.

- **Valvular heart diseases**

Like degenerative aortic stenosis and mitral & aortic regurgitation

- **Arrhythmias like atrial fibrillation with rapid ventricular response**

No Hx of palpitation, abnormal heartbeat and dizziness

- **Smoking**

Scanned with CamScanner

As I described earlier that patient is ex-smoker with 20-pack year, however, he has quit the smoking 2 years back

- **Cardiomyopathies**
  - **a) Dilated cardiomyopathy**

There is no Hx of **Alcohol** intake, exposure to **Chemo/radiation**, high-risk sexual behaviour &IV drug abuse (**HIV**) and Hx of photosensitivity, malar rash and oral ulcers **(autoimmune)**

  - **b) HOCM**

There is no Hx of sudden cardiac death in family

  - **c) peri-partum cardiomyopathy**

No Hx of shortness of breath, ankle swelling during pregnancy or after delivery

  - **restrictive cardiomyopathy**

There is no Hx of darkening of skin complexion, joint pain, **(hemochromatosis)**, and large size of tongue (amyloidosis), dry cough and painful skin nodules **(sarcoidosis)**.

  - **Idiopathic cardiomyopathy**

- **Ask about etiology of (this) exacerbation**
  - non-compliance to medicine and dietary advice
  - anemia
  - worsening of the diseases(primary cause of heart failure)
  - recent MI or arrhythmia
  - infection like LRTI
  - hypo or hyperthyroid

Patient denied any Hx of fever, productive cough, paleness of complexion, palpitation & dizziness, heat or cold intolerance, but admit non-compliance to medicine and ↑ intake of salt

Complications of heart failure

- **multi-organ failure (cardio-renal syndrome)**
  No Hx of decreased urine out-put, yellow discoloration of sclera
- **postural hypotension**
  No Hx of dizziness on standing
- **arrhythmias**
  There is no Hx of palpitation, abnormal heartbeat and syncopal attack
- **thrombosis (2 heart failure)→DVT**
  No Hx of using blood thinning medication or doctor has informed the patient of clotting of blood in a vessel
- **Cardiogenic shock**
  Hx of cold clammy skin, low BP that is not responding to common remedy
- **pulmonary edema**
  No Hx of sudden severe shortness of breath, pink frothy sputum and distended neck veins
- **Congestive Hepatopathy**
  Hx of pain in right hypochondrium, yellow discoloration of sclera and abdominal distension

Scanned with CamScanner

- **Complication of drugs**

  There is no Hx of dry cough, dizziness on standing (diuretics), yellowish tinge of vision and abnormally low heartbeat.

ITP (ask investigations, treatment and any procedures during current admission)

See viva section

Now ask relevant **PAM-HUG-FOSS-TV**

(Past HX like DM, HTN, and any significant pre-morbid if you did not ask in the **CARE)**

Examination:

Lying At 45°

General Inspection

- Marfan's Turner's Down Syndrome
- Rheumatological disorders – Ankylosing
- Spondylitis (aortic regurgitation)
- Acromegaly and SOB
- Temperature chart (endocarditis)

Hands

- Radial pulses – right and left
- Radio femoral delay (if indicated)
- Clubbing
- Signs of infective endocarditis-splinter
- Haemorrhage, Osler's nodes, etc.
- Peripheral cyanosis
- Xanthemata

Blood Pressure

Face

Eyes:

Cornea: arcus cornea

Sclera: pallor, jaundice

Pupils: Argyll Robertson(aortic regurgitation)

Xanthelasma

Malar flush (mitral stenosis, pulmonary stenosis)

Mouth:

Cyanosis

Palate (high arched-mar fan's)

Dentition

.Neck

Jugular venous pressure:

Central venous pressure height

Wave from (especially large v waves)

Carotids:

Pulse character

Precordium

- Inspect:

  Scars-whole chest, back

  Deformity
- Apex beat – position, character

  Abnormal pulsations
- Palpate:

  Apex beat → position, character and Thrills

  Abnormal impulses
- Auscultate →Heart sounds and murmurs

Position patient left lateral position siting forward (forced expiratory apnoea)

- Dynamic auscultation:
- Respiratory phase's Valsalva manoeuvre
- Exercise (isometric e.g. handgrip)

Sitting forward

Back

Scars, deformity

Sacral edema

Pleural effusions (percuss and auscultate)

Lying flat –

Abdomen

Palpate liver (pulsatile, etc.), spleen, and

Scanned with CamScanner

aorta

Percuss for ascites (right heart failure)

Femoral arteries – palpate, auscultate

Legs

Clubbing toes

Cyanosis, cold limbs, trophic changes, ulceration (peripheral vascular disease)

All peripheral pulses

Edema

Xanthomata

Calf tenderness

Other

Fundi Roth spot in (endocarditis)

Based on history and clinical examination, my clinical diagnosis is (or DDs are)

- Heart failure precipitated by non-compliance of medicine
- Heart failure .....by worsening of ischemic heart disease
- Heart failure .....by chest infection

Scanned with CamScanner

VIVA

How will you investigate this patient

Baseline investigations

CBC→ Hb,RDW,TLC, TLC, ↓ platelets

ESR, CRP→ for infective exacerbation

LFT→ ALT↑MOF or congestive Hepatopathy

RFT→ deranged RFT may signify MOF or heptorenal syndrome or shock

serum electrolyte→ fluid overload and diuretics (↓NA)

- **chest x-ray →**cardiomegaly ,fluid overload
- **oximeter&ABG→** hypoxia and resp alkalosis

Specific investigation

- **ECG→**LVH,RVH,arrythmias and ischemic changes
- **ECHO→** systolic or diastolic dysfunction
- **BNP** >100pg/mL and pro BNP>300pg/mL are significant **(only during acute decompensated heart failure and not in chronic stable heart failure)**
- **TFTs→** Hyper+hypo both can cause acute decompensation
- **Iron studies→** hemochromatosis
- **coronary angiography→**IHD
- **Radionuclide angiography and cardiac MRI→** measure LV ejection fraction and analysis of regional wall motion
- **MRI scan →**for presence of scar tissue and infiltrative diseases
- **cardiac catheterization →** invasive test for ,presence and extent of CAD
- **Stress echocardiography→** to see inducible wall motion abnormalities under stress
- **thallium stress test →**it shows ,how well blood flows into heart while you are exercising or at rest and scarring of heart muscles due to previous MI(e.g. viable tissue , heart tissue prone to necrosis and dead tissue) .

- **The most useful test is the ECHO because it can differentiate heart failure with and without preserved LV systolic function.**

US classification of heart failure stages

- **stage A→** patient at risk of heart failure(like hypertensive patients)
- **stage B→** Patient who have structural heart disease but not no current or previously recognized symptoms of heart failure (like patient with previous MI, other causes of reduced systolic function ,LVH, or asymptomatic valvular disease)
- **stage C→** patient with clinical heart failure
- **stage D→** heart failure refractory to usual therapy

NYHA Classification of Heart Failure

This classification is important since some of the treatments are indicated based on NYHA classification

- **class i** (asymptomatic
- **class ii** (symptomatic with moderate activity)

Scanned with CamScanner

- **class iii** (symptomatic with mild activity)
- **Class IV** (symptomatic at rest)

What are the Findings That Favours Heart Failure as the Cause of Dyspnoea?

- History of myocardial infarction
- No wheeze
- Paroxysmal nocturnal dyspnoea (PND)
- Orthopnoea
- Cough only on lying down
- Abnormal apex beat
- Third heart sound (S3)
- Mitral regurgitant murmur

Treatment

- **Heart failure with reduced left ventricular ejection fraction(LVEF)(HfrEF)**

- **aims of treatment**

  Reliving symptoms, improving functional status and preventing death & hospitalization

- **correction of reversible cause like**

the major reversible causes of heart failure with reduced LVEF,(chronic systolic heart failure) include valvular lesions, myocardial ischemia ,uncontrolled hypertension ,arrhythmia, thyroid disorder , intracardiac -shunts ,high-output states and alcohol or drugs-induced myocardial depression .

A.pharmacologic treatment

Drugs with mortality benefits

➢ **ACE INHBIOTRS**

- ↓ mortality by 20% in symptomatic heart failure
- most trial ACE is ramipril
- other ACE indicated for HfrEF are captopril, Enalapril, lisinopril and trandopril

➢ **ARBs**

- While they have the same level of recommendation in the guidelines, generally ACE inhibitors are preferred over ARBs for patients who tolerate them
- Candesartan or valsartan provides important benefits as alternative to ACE inhibitors in chronic heart failure with reduced LVEF.

➢ **Beta-Blocker**

- three medications have strong evidence of reducing mortality like **carvedilol** (non-selective beta-1 and beta-2 receptor blocker) ,extended -release **metoprolol succinate** (beta-1 selective) and **bisoprolol**(beta-1 selective)
- stable patients(defined as having no recent deterioration or evidence of volume overload) with mild, moderate and even severe heart failure should be treated with a beta-blocker unless there is a noncardiac contraindication
- patients should be instructed to monitor their weight as indicator of fluid retention

Scanned with CamScanner

➢ **Aldosterone Antagonist**

- spironolactone (25→50mg) and eplerenone(25→50mg) showed a 29% ↓ mortality and other clinical endpoints

➢ **Combination sacubitril and valsartan**

(24mg/26mg, 49mg/51mg, 97mg/103mg)

- the most recently approved medication for HfrEF
- the combination regimen is called angiotensin receptor-neprilysin inhibitor (ARNI)
- ARNI ↓ cardiovascular death and hospitalization by 20%
- Class 1 recommendation by ACC/AHA and the ESC guidelines for the use of sacubitril/valsartan **as replacement** for ACE inhibitors for patients with HfrEF who **remain symptomatic** on an ACE, Beta-Blocker and mineralocorticoid inhibitor.

➢ **SGLT2 inhibitor**

- SGLT2 substantially reduce the risk of cardiovascular death and hospitalization for patients with HfrEF with or without diabetes
- Dapagliflozin has been approved for HfrEF by FDA while empagliflozin is under review.

Drugs used in heart failure without mortality benefits

➢ **Digitalis glycosides(Digoxin)**

- It should be used when patients remain symptomatic despite maximum tolerated medicine
- strongly indicated in heart failure who are in atrial fibrillation
- oral loading dose is 0.75-1.25mg daily and maintenance dose is 0.125-.025mg
- ½ life is 24-36 hours and eliminated via kidney
- Notorious for drug interaction (like amiodarone, quinidine, verapamil etc.) and its optimum plasma level is 0.7-1.2ng/mL.

➢ **Diuretic therapy**

- Diuretics are the most effective means of providing symptomatic relief to patients with moderate to severe heart failure with dyspnea and fluid overload, for heart failure with either reduced or preserved LVEF.
- for mild fluid retention , **thiazide diuretics or similar agent** may be used .(metolazone 2.5-5mg , chlorthalidone 25-50mg and hydrochlorothiazide 25-100mg)
- for severe fluid overload ,**loop diuretics** should be used .(furosemide 20-320mg ,bumetanide 1-8mg and torsemide20-200 mg/day)

➢ **nitrates & hydralazine**

- combination of hydralazine & isosorbide dinitrate improve outcomes in African Americans but the effects are less clear than that of ACEs

- **New drugs (Recent Advances in HfrEF)**

➢ **Ivabradine**

(5mg DB→7.5mg BD)

- **inhibits the I**$_f$channel in the sinus node

Scanned with CamScanner

- US and the European guidelines give it a class IIa recommendation for patients in sinus rhythm with a heart rate of 70 beats/min or more with an EF of 35% or less and persistent symptoms despite treatment with maximum tolerated dose of Beta-blocker ,ACES or ARBs and an aldosterone antagonist

➢ **Vericiguat(a soluble CGMP stimulator)**

- It reduces the risk of cardiovascular death and heart failure hospitalization in chronic heart failure patient with ejection fraction < 45%. Initial dose is 2.5 mg once a day and titrate to 10 mg (maximum dose) once daily.

Drugs that should be avoided in HfrEF patients

- Glitazones, most calcium channel blockers (except amlodipine and felodipine), NSAIDs, COX2 inhibitors and combination of ACEs, ARBs and aldosterone (↑risk of hyperkalaemia).

B.Non-pharmacologic treatment

➢ **implantable cardioverter defibrillators (ICD)**

Indication include

- symptomatic or asymptomatic arrhythmia
- Chronic heart failure and LV systolic dysfunction (EF<35%)

Who receive optimum treatment?

- VT/VF survival of cardiac arrest

➢ **Biventricular pacing (cardiac resynchronization therapy CRT)**

Criteria

- NYHA ii ,iii and ambulatory class IV heart failure
- EF≤ 35%
- LBBB with QRS duration of ≥120 msec
- Patients with non-left bundle branch block pattern and prolonged QRS duration may be considered for treatment

➢ **coronary revascularization**

Revascularization warranted for some patient with heart failure including those with more severe angina or left main coronary disease

➢ **Cardiac transplantation**

- indicated if patient is still symptomatic despite all measures
- one –year survival is 80-90%
- five –year survival is > 70%

➢ **Ventricular assist device**

- it can be used in patients who require ventricular support either to allow the heart to recover or as a bridge to transplantation

➢ **heart failure with atrial fibrillation**

- Rx is anticoagulation and digoxin (loading dose 0.75-1.25mcg while maintenance dose is 0.125-0.25mcg)

➢ **role of statin in HF(without DM ,HTN)**

Scanned with CamScanner

- no role

➢ **indication of anticoagulation in heart failure without atrial fibrillation**

- EF<35%
- Lt-atrial >4cm
- AWMI

➢ **HEART FAILURE WITH PRESERVED LVEF**

- no therapy so far have been shown to improve survival in this specific population
- Treatment is Beta-blocker, diuretics and spironolactone (BDS) and to treat comorbidities like diabetes, Hypertension.
- **Ventricular assist device**
- it can be used in patients who require ventricular support either to allow the heart to recover or as a bridge to transplantation

➢ **Prognosis of heart failure**

- HfrEF carries poor prognosis
- even with appropriate treatment, the 5-year mortality is 50%

➢ **Poor prognostic factors**

- old-age
- lower LVEF
- MOF
- more severe symptoms
- chronic kidney disease & diabetes
- anemia &↓ Na
- ↑uric acid& RDW

○ **Acute Heart Failure and Pulmonary edema**

Major causes

- exacerbation of chronic heart failure
- acute massive MI
- Acute severe hypertension
- volume overload of LV(valvular regurgitation) and mitral stenosis

- most common presentation in developed world is acute or sub-acute deterioration of chronic heart failure precipitated by discontinuation of medication ,↑salt intake , myocardial ischemia , tachyarrhythmias(esp. rapid atrial fibrillation), or intercurrent infection
  - while noncardiac causes of pulmonary edema include intravenous opioids, ↑intracranial pressure , high altitude , sepsis ,medications ,inhaled toxin ,transfusion reaction ,DIC and shock .

○ **Management of pulmonary edema**

- **prop-up position** with legs dangling over the side of bed
- **oxygen inhalation** and if needed non-invasive pressure support ventilation → endotracheal intubation and mechanical ventilation

Scanned with CamScanner

- **Morphine is** highly effective as it ↑ venous capacitance, ↓ LA pressure and relive anxiety (2-8mg IV and repeat after 2-4 hrs.)
- **intravenous diuretics** furosemide 40mg or high dose and bumetanide 1mg or higher dose .these agents produce venodilation before the onset of diuresis (higher doses in patient who are on long-term diuretic therapy 80 × 2.5 times).
- **Nitrate therapy** it improve symptoms by↓ BP and LV filling pressures (pre-load). Intravenous, sublingual, topical will improve the symptoms.
- **Nitrates are particularly valuable in patients with accompanying hypertension.**
- **intravenous nesiritide(recombinant human BNP**
- **(Recent advances)**
  It is potent vasodilator that reduces ventricular filling pressure and improves cardiac output .dose is 2mcg/kg/min by IV bolus followed by an infusion of 0.01 mcg/kg /min. Major side effect is hypotension
- **intravenous milrinone(phosphodiesterase PD-3 inhibitor)**
- **(Recent advances)**
  It is positive inotrope with little chronotropic effect and direct vasodilator (↓ pre and afterload)
- **Dobutamine infusion**
  As an inotropic agent in HF
- **Intra-Aortic Balloon Pump(IBAP)**
  Heart failure resistant to triple inotropic support and there is no contraindication
- **Dialysis**
  If pulmonary edema (due to fluid overload) is not responding to any therapy.
- bronchospasm may occours in pulmonary edema and may worsen hypoxemia so it should be treated with inhaled beta-adrenergic agonist or iv aminophylline but this may provoke tachycardia and supraventricular arrhythmias

JUGULAR VENOUS PRESSURE (JVP)

Causes of an elevated central venous pressure (CVP)

- Right ventricular failure
- Tricuspid stenosis or regurgitation
- Pericardial effusion or constrictive pericarditis
- Superior vena caval obstruction
- Fluid overload
- Hyperdynamic circulation

Waveform

Causes Of a Dominant A Wave

- Tricuspid stenosis (also causing a slow y descent)
- Pulmonary stenosis
- Pulmonary hypertension

Causes Of Cannon A Waves

Scanned with CamScanner

- Complete heart block
- Paroxysmal nodal tachycardia with retrograde atrial conduction
- Ventricular tachycardia with retrograde atrial conduction or atrioventricular dissociation

Causes of a Dominant V Wave

- Tricuspid regurgitation

X DESCENT

- Absent: atrial fibrillation
- Exaggerated: acute cardiac tamponade, constrictive pericarditis

Y DESCENT

- Sharp: severe tricuspid regurgitation, constrictive pericarditis
- Slow: tricuspid stenosis, right atrial myxoma

Clinical trials

- **RALES trial** →spironolactone 25 mg ↓ mortality by 29% in heart failure
- **PARADIGM HF**→ combination of sacubitril and valsartan ↓ mortality by 20%
- **COMET trial** → significant reduction in all-cause mortality and cardiovascular mortality by carvedilol

Scanned with CamScanner

APPROACH TO FEVER OF UNKNOWN ORIGIN (Infective endocarditis)

P/C

Fever -1month

HOPI (ODPARA)

patient presented with fever that is gradual in-onset, intermittent in pattern, progressive in nature and one month in duration .it has no specific timing and may occours any time of the day and night .It is documented and maximum documented temperature is .....initially it was relived with antipyretic but fit is or the last ---days not relived with antipyretic, however it has no aggravating factors .it is associated with lethargy ,and sometime sweating at night . **However, there is no history of**

- **SYSTEMIC REVIEW** (to search for source of infection from head to toe)
  - **CNS**
    No Hx of headache, altered sensorium, photophobia and fits
  - **EYES**
    No Hx of redness, discharge
  - **ENT**
    No Hx of ear or nasal discharge, postnasal drip, sore throat and HX of pain on touching the face **(sinusitis)**
  - **thyroid**
    No HX of neck swelling moving with swallowing, heat& cold intolerance
  - **chest**
    no Hx of dry or productive cough ,blood in sputum , shortness of breath on exertion or lying flat , a wheezy chest sound , chest pain and pedal edema .
  - **Abdomen**
    No HX of abdominal distension, abdominal pain, heaviness in RHQ/LHQ, loose motion
  - **Genitourinary system**
    No Hx of flank pain, blood in urine, burning micturition, ↑urinary urgency and frequency
  - **MSK(autoimmune disorder)**
    No Hx of palpable skin rash, joint pain, oral ulcer, hair loss and blood in sputum and urine
  - **Brucellosis**
    No Hx of contact with animal or ingestion of unpasteurized milk
  - **Psittacosis/malaria /Dengue /legionella**
    No Hx of ill birds, mosquito bites, and intake of water from storage tanks
  - **HIV**
    No Hx of Iv drug abuse and high-risk sexual behaviour
  - **TB**
    No Hx of contact with TB patient
  - **syphilis/HSV/behcets**
    No Hx of oral or genital ulcerations
  - **Rheumatic heart disease**

Scanned with CamScanner

- no Hx of monthly intramuscular injection
- **malignancy**
  Hx of weight loss, ↓ appetite, lumps and bumps in the body

○ **Infective endocarditis (IE)**

CARE OF IE

- no Hx of IV drug abuse and high risk sexual behaviour
- no Hx of congenital heart diseases, monthly use of intramuscular injection and recent cardiac surgery
- no Hx of recent instrumentation like endoscopy ,bronchoscopy
- no Hx of altered bowel habit , weight loss and blood in stool
- no Hx of joint pain /oral ulcer and skin rash
- no Hx of ↓ appetite, lumps & bumps and positive family history of cancer
- no Hx of contacts with animals and intake of unpasteurized milk
- no Hx of multiple IV Cannulation, however **there is positive Hx** of multiple dental extraction few weeks back

Complications of IE

- Hx of weakness of any part of the body
- Hx sudden loss of vision in one eye
- Hx of painful red spot on skin **(vasculitis)**
- Hx of blood in urine or sputum **(GN)**
- Hx of sudden severe shortness of breath , pink frothy sputum production (**pulmonary edema due to mitral regurgitation**
- HX of septic emboli (to any part of body like sudden severe abdominal pain due **splenic infarct**, sudden severe chest pain (due to **lung abscess or infarct**), aortic root abscess and mycotic aneurysm etc.)
- Hx of palpitation, shortness of breath while lying flat and disturbed night sleeps that improve on prop-up position **(HF)**.

ITP (Investigations, treatments and procedures) for IE or any of risk factor

Now ask relevant

Relevant PAM-HUGS-FOSS-TV-F

Scanned with CamScanner

EXAMINATION

General look → ill looking or toxic look

GPE→ clubbing , splinter haemorrhage , Osler node ,janeway lesions(palms and soles).Pulse , BP ,purpura ,Temp ,venepunctures for IV drug abuse, JVP, anemia ,jaundice ,lymphadenopathy

Systemic Examination → same as outlined in heart failure including

- neurological →look for neurological deficit and involuntary moments like Sydenham chorea
- abdomen →splenomegaly , tender hepatomegaly and ascites due to RT heart failure
- chest →crackles and effusion due to heart failure or septic emboli
- fundascopy→ Roth spots

Scanned with CamScanner

VIVA OF Infective Endocarditis

HOW WILL YOU DIAGNOSE IE?

Modified Duke Criteria

i. Pathological Criteria

Positive histology or culture from pathological material obtained at autopsy or cardiac surgery

ii. clinical criteria

Major Criteria

Two positive blood cultures with typical organism

Persistent bacteraemia

Single Positive serology for coxiella (or anti-phase 1 IgG antibody titer ≥ 1:800)

Positive **echocardiogram like**

1. Vegetation
2. Abscess Or
3. New Regurgitation Or
4. Dehiscence of Prosthetic Valves

Minor Criteria

Predisposing heart disease or IV drug abuse

Fever >38%

Immunological phenomena (GN, Osler nodes, Roth spots)

Vascular phenomena (janewaylesions, MI, stroke cutaneous haemorrhage, aneurysm, systemic emboli and pulmonary infraction)

Microbiological evidence not fitting major criteria

- A definite diagnosis of can be made with 80% accuracy if two major criteria or one major criteria and three minor criteria or five minor criteria are fulfilled .while possible diagnosis of IE is made if one major and one minor or three minor criteria are meet .

Blood culture

- 3 sets of blood cultures are recommended before antibiotics
- each culture bottle should be filled with 10mL of blood since half of the adults have less than 1 colony forming unit of bacteria per mL blood
- optimal yield is with two or three sets of cultures from different sites and there is no difference in yield if blood is collected simultaneously or several hours apart

Culture negative IE

- 5% cases are culture negative
- may be due to administration of antibiotics prior to culture or due to organism that require special media for growth (e.g. **legionella , bartonella , abiotrophia species**) or organism that do not grow on artificial media (**tropheryma whipplei ,psittacosis or pathogen of Q fever**) or those that may require prolong incubation (e.g. **HACEK group ,Brucella and anaerobes**).**Bartonella quintana** is also an important cause of culture –negative endocarditis . Therefore, serology or PCR of the suspected organism and workup for autoimmune disorder or hidden malignancy should be carried out.

Scanned with CamScanner

Investigations of IE

- 3 sets of blood culture from 3 different sites irrespective of time
- transthoracic ECHO(55-65% sensitivity) while trans esophageal ECHO(90 %sensitive)
- **ECG→** conduction abnormalities may suggest myocardial abscess formation
- **CRP→ CRP (qualitative)monitoring as effectiveness of therapy**
- **serology /PCR** of HACEK, fungus etc. and when patient is already on antibiotics
- **CXR→**may show evidence for underlying cardiac abnormalities. Pulmonary edema in left-sided disease, pulmonary emboli/abscess in right-sided disease.
- **Full Blood Count** reduced hemoglobin increased white cells, increased or reduced platelets.
- **urea and electrolytes** increased urea and creatinine
- **liver biochemistry** increased serum alkaline phosphatase
- **urine :**proteinuria and haematuria
- **colonoscopy →** S.bovis

Clinical Features of Infective Endocarditis

Clinical feature	approximate
General	
Malaise	95
Clubbing	10
Cardiac	
Murmurs	90
Cardiac failure	50
Arthralgia	25
Pyrexia	90
Skin lesions	
Osler nodes	15
Splinter haemorrhages	10
Janeway lesions	5
Petechiae	50
Eyes	
Roth spots	5
Conjunctival splinter haemorrhages	Rare
Splenomegaly	40
Neurological	
Cerebral emboli	20
Mycotic aneurysm	10
Renal	
Haematuria	70

Scanned with CamScanner

What are the Procedures where I.E. prophylaxis needed?

- all dental procedures that involve manipulation of gingival tissue or the periapical region of the teeth or perforation of the oral mucosa
- respiratory tract procedures that involves incision of the respiratory tract (Biopsy)
- procedures on infected skin, skin structures or musculoskeletal tissue
- while GI& genitourinary procedures (without biopsy) and other condition **does not need** IE prophylaxis

What are the cardiac conditions with high risk of adverse outcomes from endocarditis for which prophylaxis with dental procedures is recommended?

- prosthetic heart valve
- previous infective endocarditis
- congenital heart disease like

a) unrepaired cyanotic heart disease including palliative shunts and conduits
b) Completely repaired congenital heart defect with prosthetic material or device, whether placed by surgery or by catheter intervention, during the first 6 months after the procedure repaired congenital heart disease with residual defects at the site or adjacent to the site of a prosthetic patch or prosthetic device.

Cardiac transplantation recipients in whom cardiac valvulopathy develops

What is the recommended regimen for prophylaxis of IE for eligible candidates?

- **oral regimen**
- amoxicillin 2g 1 hour before procedure
- **for penicillin allergic patient**
  - clindamycin 600mg 1 hour before the procedure or
  - cephalexin 2g (contraindicated if there is history of a beta-lactam immediate hypersensitivity)
  - azithromycin/clarithromycin 500mg before the procedures
- **parenteral**
- ampicillin 2g IM OR IV half hr. before the procedure
- **penicillin allergic patients**
  - Clindamycin 600 mg IV 1 hr. before..... or
  - cefazoline 1g half hr. before (contraindicated if there is history of a beta-lactam immediate hypersensitivity)

How will you treat IE?

- Empirical treatment followed by culture based treatment. **empirical therapy(native valve) include**
  - vancomycin 1g BD plus ceftriaxone 1g BD± gentamycin 2mg /kg

Culture Based Treatment of IE

1) Stap-aureus

- **Methicillin –susceptible s aureus**

Scanned with CamScanner

- ➢ →nafcillin/oxacillin 12g or cefazoline 6g IV daily in divided doses (or continuously) or
- ➢ → ceftriaxone(or penicillin G 18 million units OD)+ gentamycin for 2-4 weeks

- **methicillin resistant s aureus(MRSA)**
  - **native valve**

    →vancomycin 1gram +gentamycin 3mg for 4 weeks
  - **prosthetic valve**

    → vancomycin +rifampicin (300mg 8 hourly) for 6 weeks along with gentamycin 3mg (8 hourly)for the first 2 weeks

2) **Enterococci (group D streptococci)**

   →ampicillin (2g IV 4 hourly) or penicillin G 18-30 million units (continuously or in 6 divided doses) plus gentamycin 1mg/kg (TDS) or

   →ampicillin (2g IV 4 hourly) and ceftriaxone (2g IV BD).this regimen is recommended when creatinine clearance < 50 mL/min or whose enterococci are resistant to gentamycin. The recommended duration of therapy for both regimens is 4-6 weeks.

   → Vancomycin and gentamycin **for ampicillin resistant** enterococci

3) **other streptococci (like S pneumonaie, S gallolytics ,group streptococci A,B,C and G)**

   → High dose penicillin (24 million units), ceftriaxone and gentamycin

4) **HACEK organisms**

   →treatment of choice is ceftriaxone 2g OD for 4 weeks and in case of prosthetic valve for 6 weeks .alternative is

5) **Fungal infection**

   →amphotericin and 5-flucytosine followed by Voriconazole for 6-8 weeks

6) **legionella**

   → Fluoroquinolones and rifampicin for 6 weeks

7) **Mycoplasma**

   → Fluoroquinolones for 6 weeks

8) **non-infective etiology**

   →treat the underlying cause

What are the indications for surgery in IE?

A) acute heart failure unresponsive to medical therapy is indication for valve replacement even if active infection is present
B) infection that is unresponsive to appropriate antimicrobial therapy after 7-10 days (like persistent fever & bacteremia)
C) fungal endocarditis
D) septal abscess and when infection involves sinus of valsalva
E) recurrent embolization even when infection is responding
F) large and fragile vegetation

Scanned with CamScanner

Treatment of the complications

A) Stroke 2 to I.E

No antiplatelet for at least 2 weeks. In patients with S aureus prosthetic valve endocarditis complicated by an embolic stroke, anticoagulation should be discontinued for the first 2 weeks .

B) Mycotic aneurysm

Antifungal and surgical debridement

C) Glomerulonephritis

Steroid and cyclophosphamide

What are the risk factors for systemic embolization (ECHO predictors)

1) multiple vegetations
2) vegetation> 1cm or growing size of vegetation
3) penduculated or mobile vegetation

Prognosis of I.E

- with treatment mortality is 20-25% while without treatment it is almost 100%
- streptococci cure is 90% while staph aureus is 70%

Poor prognostic factors

- old age and comorbid conditions
- aortic valve involvement
- multiple valve endocarditis
- I.E with complication
- prosthetic valve endocarditis

Acute I.E

High-grade fever, toxic look caused by → staph aureus

Sub -acute I.E

Low-grade fever and weight loss caused by→ viridians streptococci

Scanned with CamScanner

APPROACH TO PALPITATION (Rheumatic Heart Disease)

P/C

Patient may present with 3 complaints

- SOB
- Palpitation ---------- 2 months
- weakness of body (stroke)

Approach to shortness of breath has already been discussed and for weakness of any part of the body see neurology section

ODPARA (HOPI)

Patient presented with palpitation that is sudden in onset, 2 months in duration and episodic in nature .patients described palpitation as racing of the heart that is regular in pattern. Initially, it was during exertion like playing that lasted 10-20 minutes and resolved during rest .However, with due time palpitation occours even on rest that last almost more than 30 minutes and resolve spontaneously and (or with medicine). It has no association with tea, coffee and drinks and does not relived now with medicine of a local doctor. **However patient denies**

DDs of Palpitation

1) Heart

- **Heart failure**

No Hx of body swelling, distended neck veins, shortness of breath while lying flat and disturbed night sleep

- **M.I**

No HX of sudden severe left sided chest pain that is associated with nausea and sweating on background of sedentary lifestyle, smoking DM and HTN.

- **congenital valvular heart disease**

No family HX of congenital heart disease

- **infective endocarditis**

No Hx of fever, weight loss, recent HX of surgery and instrumentation of the body

- **Rheumatic heart disease**

Long case here

2) Resp

- **pneumonia**

No Hx of fever associated with rigors and chills and rusty color sputum

- **chronic thromboembolism**

No HX of prolong immobilization, travel and swelling of lower limb.

- **Inhaler (salbutamol)**

No HX of inhaler use for wheezy chest, cough and shortness of breath

3) GIT

- **Carcinoid**

No Hx of loose motion associated with episodic shortness of breath and facial flushing.

- **Electrolyte imbalance**

No HX of loose motion, vomiting and excessive sweating

4) Endocrinology

- **Pheochromocytoma**

Scanned with CamScanner

No HX of episodic headache, tremor and ↑BP

- **Hyperthyroidism**

No HX of heat intolerance, tremors and weight loss

- **carcinoid**

See above

- **Addison**

No HX of blackening of complexion, vomiting and dizziness on standing

- **Hypoglycaemia**

No HX of cold sweating, blurring of vision on background of diabetes or chronic live disease

5) Haematology

- **Anemia**

No HX of pallor of complexion, easy fatigability or blood loss

6) Drugs

No HX of intake of recreational &anti-arrhythmic drugs, diuretics and thyroxin

7) psychological

There is no HX of psychological problems like stress and anxiety etc.

Always exclude few important relevant DDs only

CARE of rheumatic heart disease (ask all revised Jones criteria questions)

- patient denied repeated childhood throat infection
- patient denied migratory joints pain
- patient denied skin rash ,skin nodules or any abnormal or involuntary movements of any part of the body

- **clues pointing to rheumatic heart disease**
- HX of monthly intramuscular injection
- HX of prolong use of antibiotic twice a day (erythromycin 250mg BD)
- HX of valvular replacement or suggestion of valvular replacement by a doctor
- HX of blood thinning medication like warfarin
- **in 40% cases** of rheumatic heart disease have **no evidence** (of rheumatic fever)therefore if patient denies all clues suggestive of rheumatic heart disease , still there is **possibility of** rheumatic heart disease

ITP (investigations, treatment and procedures**)**

Scanned with CamScanner

Relevant

PAM-HUGS-FOSS-TV-F

- **Socioeconomic** HX is important. It is more prevalent in developing countries (low socioeconomic class).

Examination scheme

GPE →temp, pulse (irregular), BP, JVP and malar flush

While systemic examination is same as outline for heart failure including clinical features like chorea /subcutaneous nodule) suggestive of rheumatic heart disease. During cardiovascular examination, if finding **suggestive of MS** you **must exclude** all possible causes of MS (like RHD, congenital, carcinoid and autoimmune etc.) likewise **exclude all** causes of **MR, AS and AR** once you get clue of the underlying heart lesion .

CNS→ search for any neurological deficits

Resp → signs of heart failure and pulmonary HTN

Abdomen → see for signs of RT heart failure

Scanned with CamScanner

VIVA OF RHEUMATIC HEART DISEASE

What is revised Jones criterion?

The 2015 revised jones criteria

Population	Criteria	
	Major	Minor
Low risk	Carditis (clinical or subclinical)	Polyarthralgia
	Arthritis (polyarthritis only)	Fever (≥ 38.5c)
	Chorea	ESR≥60 mm/h or CRP≥3.0mg/dl (or both)
	Erythema marginatum	Prolonged PR interval (unless carditis is major criteria
	Subcutaneous nodules	
Moderate and high risk	Carditis (clinical or subclinical)	Monoarthralgia
	Arthritis (monoarthritis, polyarthritis Polyarthralgia)	Fever(≥ 38C)
	Chorea	ESR≥ 30 mm/h or CRP ≥ 3.0 mg/dL or both
	Erythema marginatum	Prolonged PR interval(unless carditis is a major criterion
	Subcutaneous nodules	

Evidence of preceding streptococcal infection

- rising anti-streptolysin O titer or streptococcal antibodies (anti-DNase B)
- Positive throat culture for group A beta-hemolytic streptococcal or A positive rapid group A streptococcal carbohydrate antigen test in a child with high probability pharyngitis.

What is the causative agent of rheumatic heart disease?

Group A beta hemolytic streptococci

What is the incubation period?

→ 2-5 weeks

Pathology →characteristic lesion is perivascular granulomatous reaction with valvulitis→ Aschoff nodules.

The clinical feature of infection include in descending order

- carditis(50-70%) include pericarditis ,cardiomegaly detected by x-ray or echo ,heart failure and acute mitral or aortic valvular regurgitation
- Arthritis (35-66%)
- Chorea (10-30%)
- Subcutaneous nodules (0-10%)
- Erythema marginatum (<6%)

Mitral valve is acutely attacked in 70-80% of cases, aortic valve in 30% while tricuspid and pulmonic valve in less than 5 % of cases.

How will you treat acute rheumatic fever?

Scanned with CamScanner

- The patient should be advised **strict bed rest** until the temperature return to normal (without the use of antipyretic medications) and the ESR, resting pulse rate and ECG have all returned to baseline
- **Joint pain**→ salicylates like aspirin markedly improve fever and relive joint pain and swelling .However, it has no effect on natural course of the disease. Adult may require large doses of aspirin 0.6 ---0.9 g every 4 hourly.
- **Antibiotic** →penicillin like benzathine penicillin **1.2 million units** IM once or procaine penicillin 600,000 IM OD for 10 days .in case of penicillin sensitivity ,**erythromycin** (40mg/kg/day)may be used
- **Corticosteroid**→ it does not prevent or minimized cardiac damage .a short course of steroid (40-60mg tapper over 2 weeks) is usually cause rapid improvement of the joint symptoms where patient is intolerant to salicylates or when it is ineffective.
- **Treatment of complication** like acute heart failure.

How to check effectiveness of treatment?

→By CRP level

Chronic rheumatic heart disease

chronic rheumatic heart disease result from single or repeated attacks of rheumatic fever that produces rigidity and deformity of the valve cusps ,fusion of the commissures ,or shortening and fusion of the chordae tendiane. This result in valve stenosis or regurgitation or both. In chronic rheumatic heart disease , the mitral valve alone is affected in 50-60% , combined lesion of aortic and mitral valve occur in 20% while pure aortic valve lesions are less common and tricuspid (10%)& pulmonic valve lesion are less common .

How will you treat rheumatic chorea?

It is self-limiting and does not need treatment, however if it is refractory and protracted than it should be treated with **Epival.**

Mitral stenosis 2 chronic rheumatic heart disease

- *normal mitral valve area(MVA) is 4-6 cm^2*
  - progressive MS ,MVA is >1.5 cm^2
  - severe MS,MVA is ≤1.5cm^2
  - very severe MS , MVA is ≤1.0 cm^2
- tapping apex beat (only in MS) is due to loud first heart sound
- loud first heart sound in MS is due to sudden slammed shut of mobile mitral valve during systole
- opening snap is produced due to sudden opening of mitral valve as a result of high-pressure gradient between left atrium and left ventricle and this signify that valve cusps are pliable and not rigid or calcified .

Scanned with CamScanner

Mitral facies or mitral flush (reddish coloration of malar prominence) is due to arteriovenous anastomoses.

For detail discussion on **MS** plz see cardiology short cases.

Prophylaxis

Primary prophylaxis

Based on **Centor** criteria (if score>2) primary prophylaxis is advised. A single intramuscular injection of benzathine penicillin is recommended. Alternative regimen is azithromycin 500mg for 5 days or Amoxil 500 mg BD is advised for 10 days.

Modified Centor Criteria

Fever	1
Tonsillar Exudate	1
Absent Cough	1
Anterior Cervical LAD	1
Age →3-14 years	1
Age 15-44 years	0
Age > 44 years	−0

Secondary prophylaxis

- if no carditis →prophylaxis for 5 years or 21-year of age whichever last longer
- if carditis with no residual heart defect →prophylaxis for 10 years from attack of rheumatic fever or 21-year of age whichever last longer
- if carditis with residual heart (valvular) defect →prophylaxis for 10 years from attack of acute rheumatic fever or 40-year of age whichever last longer.

Why 40-year?

because the peak incidence of the disease occours b/w 5-15 years and rheumatic fever is rare before age 4 years and after age 40 years .

Secondary Prophylaxis regimen

- IM monthly benzyl penicillin (1.2 million units for > 70/kg and 0.6 million units for < 70kg)
- **or erythromycin 250mg BD daily**

Rheumatic fever → chronic rheumatic heart disease takes 10-20 years.

Poor prognostic factors

- young age
- carditis as presentation
- non or poor compliance to secondary prophylaxis
- Previous episode or early recurrence.

Scanned with CamScanner

Heparin	Warfarin
½-life → 20-60 hrs.	½-life 20-60 hrs.
MOA→ anti-thrombin III	MOA→vit K antagonist
Excretion via →kidney	Excretion via→kidney
Stop→ 12hr before surgery	Stop→ 5 days before surgery
Restart → 12hr after surgery	Restart →depend on surgical risk but usually 12-24 hrs.

Scanned with CamScanner

APPROACH TO BLOOD IN VOMITUS Upper GI Bleed Due To Chronic Liver disease

P/C

Blood in the vomitus 1 day

HOPI (ODPARAV)

My patient who is normotensive normoglycemic and known case of HCV for the last 20 years (or alcoholic for the last 15 years) presented with blood in the vomitus that was sudden in onset, episodic in nature and one day in duration. My patient experienced 8 episodes in the last 24 hours .each episode contain almost half cup blood that was fresh ,bright red and very few clots .it has no exacerbating and reliving factors .it was associated with 2 episode of black tarry stools that was foul smelling and difficult to flash . **However, there is no Hx of**

Now exclude DDs of upper Gi bleeds

- **Peptic ulcer disease (35-50%)**

No Hx of chronic epigastric burning pain associated with prolong intake of painkiller medicine and hakims medication (steroid)

- **NSAID or Alcohol induced gastritis (10-20%)**

No HX of epigastric pain associated with painkiller medication or chronic alcohol intake

- **Chronic Liver Disease (2-9%)**

Long case here.see CARE

- **Portal vein thrombosis (2-9%)**

No Hx of sudden painful right hypochondrium that is painful on palpation and associated with abdominal swelling and blood in vomiting

- **Mallory –Weiss Tear (5%)**

No Hx of excessive retching followed by blood in vomiting

- **uremic gastritis**

No Hx of ↓ urine output, frothy urine, and periorbital swelling associated with these symptoms

- **CA stomach& oesophagus (2%)**

No Hx of difficulty in swallowing, unintentional weight loss lumps & bumps in the body and past Hx of malignancy.

- **Bleeding disorder / drugs induced bleeding**

Patient denied any Hx of easy brusibility, bleeding disorder or using blood-thinning medication.

- other causes include **esophagitis due to hiatus hernia**(10%) , **Vascular malformation** (5%) and **Aorto-dueodenal fistula**

Approach to black color stool

DDs of Black color stool

Same DDs as that of upper GI bleeds and including following

- **pancreatitis**

No HX of severe epigastric pain that is radiating to back

- **Zollinger-Ellison Syndrome (MEN-1 Disease)**

Scanned with CamScanner

Chronic epigastric pain not responding to stomach medications or HX of multiple ulceration of GI tract

- **↓ platelets**
  No Hx of easy brusibility and bleeding from any orifice.
- **iron tablets**
  No Hx of intake of medication containing iron supplements
- **Aortic aneurysm**
  No HX of pulsating mass in epigastrium

CARE OF CLD

- There is no HX of IV-drug abuse, blood transfusion, and tattoo, needle sharing and extramarital relationship. However, **there is positive HX of dental extraction** at a local center …. years back (**HCV &HBV**
- there is no Hx of alcoholism (**Alcohol-induced liver cirrhosis)**
- no Hx of oral ulcer ,skin rash ,hair loss and recurrent yellow discoloration of sclera (**autoimmune hepatitis**)
- there is no HX of DM , joint pain ,blackening of skin and erectile dysfunction (**Hemochromatosis**)
- No Hx of recurrent childhood chest infection associated with yellow discoloration of sclera or no HX of SOB whistling chest sound associated with liver disorder in family (**Alpha-1 antitrypsin deficiency**)
- no HX of itching , skin rash associated with these symptoms (**PBC& PSC)**
- No Hx of prolong intake of certain medicine like methotrexate ,amiodarone and methyldopa(**Drug induced liver cirrhosis)**
- no Hx of mood disorder ,tremors and fits (**Wilson disease**)
- No Hx of sudden weight loss and or weight gain **(NAFLD).**
  Hx dates back ….year when patient was diagnosed as HCV+ when he presented to a local doctors with complain of ↓ appetite and tiredness all the times .Consequently he was treated for 3 months with poor compliance and unfortunately he lost follow –up after treatment .
  - Even if patients tell you a risk factor of CLD (like he was HCV positive here), you have to exclude all major risk factor too.

Complications of CLD

- patient denied any Hx of abdominal distension ,that is tender to palpation and associated with fever(SBP)
- Patient denied Hx of heaviness in right hypochondrium and ↓ appetite (HCC)
- there is no HX of ↓ urine output (Heptorenal syndrome)
- there is no HX Of SOB on standing from sitting position (Hepatopulmonary syndrome)
- there is no Hx of skin rash and blue feet(Cryoglobulenemia)
- There is no HX of easy brusibility and bleeding from any orifice apart from blood in vomiting (Bleeding disorder)

ITP of CLD (investigations, treatment and procedure).

Scanned with CamScanner

Ask these question for current admission and in past.

Now ask relevant PAM-HUGS-FOSS-TV-F

- Never forget to ask vaccination of Hep A&B and E

Examination scheme

Orthostatic BP measurement and genitourinary examination is compulsory.

GPE temp, pulse, BP followed by appearance (hepatic facies-liver cirrhosis and puffy face-nephrotic syndrome), anemia, jaundice, cutaneous stigmata of liver disease (Leukonychia, clubbing, palmar erythema, depuytren contracture, spider navi, tattoo mark, loss of hair, and gynenomastia), lymph node, JVP and edema feet.

Systemic examination

- Abdomen: Inspection (shape, flanks, umbilicus, engorged vein, scar marks, and hernia orifice), palpation (hepatosplenomegaly and fluid thrill), percussion (shifting dullness), and auscultation (bowel sound) examine the genitalia (with prior permission) and look for loss of pubic hair , scrotal atrophy ,blood and piles due to portosystemic anastomosis
- Cardiovascular system: as per standard protocol and look for cardiac failure, desaturation on standing
- Respiratory system: Evidence of pleural effusion.
- Nervous system: Confusion, disorientation, apraxia, flapping tremor, and plantar response.

Scanned with CamScanner

VIVA OF UPPER GI BLEED

- **CBC→** Anemia may suggest chronic or sub-acute bleeding and ↓platelets may be a clue to the presence of hypersplensim in chronic liver disease.
- **urea and electrolyte→** may suggest heptorenal syndrome and elevated urea with normal creatinine concentration implies severe bleeding
- **Liver function tests →** may show evidence of chronic liver disease
- **PT ,INR →**as marker of synthetic function of liver
- **blood grouping& cross matching**
- **Ascetic tap →**Routine examination and culture
- **viral serology**
- **ultrasound abdomen →** shrunken or small liver
- **Endoscopy →** Endoscopy will yield diagnosis in 80% cases.

How will you manage this patient?

ABC approach followed by

1) **Pass 2 IV lines** and infuse crystalloid fluid to raise blood pressure.
2) **Blood transfusion (packed cell 2-4 pints)** if there is severe blood loss or there is active bleeding to achieve HB level of 7-9 g/dl.
3) **Broad spectrum antibiotic** (to cover gram negative organism) and to ↓ the risk of spontaneous bacterial peritonitis
4) **Vit –k →** 5-10mg IV if PT is > 3 times of control.
5) **Terlipressin** (↓ portal and variceal pressures by splanchnic vasoconstriction and has proven reduction in mortality) 2mg IV state followed by 2mg 4 times daily until bleeding stop followed by 1 mg 4 times daily for 72 hours. But it should be **avoided in IHD, peripheral vascular disease** and **uncontrolled** HTN.
6) **Octreotide (same MOA)** 100mcg bolus followed by 50-100 mcg /h continuous infusion until bleeding stopped or endoscopy done .it should be used when Terlipressin is contraindicated.
7) **Endoscopy**

1 it help identify the source of bleeding
2 it help determine the risk of rebleeding and guide triage
3 It renders endoscopic therapy like band ligation and sclerotherpay.

- **Esophageal varices** should be treated with band ligation if it fails **→then balloon Tamponade** (Sengdtaken –Blackmore tube will almost always stop esophageal and gastric fundal varices) while arrangement is made for a **transjugular intrahepatic portosystemic shunt** (TIPSS is also effective for gastric varices) **→ portosystemic shunt surgery** (reserved when other treatment have not been successful and are offered only to patient with good liver function) **→esophageal resection** as a last resort but operative mortality is high
- **Gastric fundal varices →** as banding is less effective so endoscopic therapy relies on injection of agents such as thrombin or cyanoacrylate glue directly into the varix to induce

Scanned with CamScanner

thrombosis. Although, highly effective cyanoacrylate injection treatment may be complicated by glue embolism to the lungs

High-risk → endoscopy within 12 hrs

(Patient with active bleeding manifested by hematemesis or bright red blood on nasogastric aspirate, shock, persistent hemodynamic derangement despite fluid resuscitation, serious medical illness and advanced liver)

Low risk → endoscopy within 24 hrs

All other patient

8) **Lactulose or phosphate enema** → 30mL/2hr until first stool then TDS (minimum 2 loose stool/day) to prevent hepatic encephalopathy.

Rebleed Risk Assessment

Rebleeding risk of upper GI bleed due to varices is assess by Rockcall score while bleed due to ulcer is estimated by forest calcification.

Rockall score

- it tell us about the risk of rebleed and mortality risk assessment for patient admitted with upper GI bleeding

Variables	Responses	Scores
Age (in years)	>60	0
	60-79	1
	>80	2
Shock	No shock	0
	Tachycardia (SBP>100mmHg,pluse> 100 beats/minute)	1
	Hypotension (SBP<100mmHg, pules > 100>beats/minute)	2
Co-morbidity	None	0
	Cardiac failure, IHD, any major co-morbidity	2
	Renal /liver failure, metastatic malignancy	3
Diagnosis (post-endoscopy)	Mallory- weiss tears	0
	All other diagnosis	1
	Malignancy of the upper GI tract	2

Scores range from 0-11 and are divided into three categories of risk

Low risk ≤2, Moderate risk 3-5, high-risk ≥6. Rockall score of < 3 have a low risk of re bleeding or death and can be considered for early discharge

Forrest classification		**Rebleeding**
Type 1	Active bleeding	
	1a spurting haemorrhage	90-100%
	1b oozing haemorrhage	80-85%

Scanned with CamScanner

Type 2	signs of recent bleeding	
	2a Non-bleeding visible vessel	40-50%
	2b adherent clot on lesion	20-30%
	2c Hematin-covered lesion	5%
Type 3	lesion without bleeding (Flat spot, clean base)	≤3%

What are the endoscopic finding (Red flags) for rebleed?

1) ↑size of varices (>5mm)
2) adherent clot
3) active bleeding vessel that is visible
4) high Child-Pugh score and active alcoholism are also risk factor for rebleeding

How will you prevent (↓ risk of) rebleeding? Or

Prevention of primary bleeding

- **Beta-blocker** (Carvedilol 6.26mg -12.5 mg /day or propranolol 80-160/day). Target heart rate is 50-55 beats/min (**55-60 beats/min**)e.g. 25 % reduction is recommended provided systolic pressure remain above 90mmHg and patient has no side effects .In patient with cirrhosis, treatment with propranolol reduces variceal bleeding by 47%, death from bleeding by 45% and overall mortality by 22%. The efficacy of beta blocker in primary prevention is similar to that of prophylactic banding .However ,meta-analysis of randomized controlled trials suggest that a combination of band ligation plus beta-blocker is superior to either variceal band ligation alone or beta-blocker alone for prevention of rebleed. Beta-blocker should be started after3- 5 days after bleed.
- **Band ligation** 90% effective for bleeding or non-bleeding varices
- **TIPS or liver transplantation**

Follow-up endoscopy

- **first episode of upper GI bleeding**

1) **no evidence** of varices on OGD → 3-year follow-up OGD
2) **Red flag of** bleeds on OGD → therapeutic band ligation 2-4 weeks apart, under the cover of proton pump inhibitor to reduce the risk of secondary bleeding from banding induce ulceration, along with beta-blocker.
3) **no Red flag** of bleeds on OGD→ yearly OGD and ± beta blocker

- **INR for endoscopy < 2.5**

  If patient is on warfarin with active bleeding and INR> 2.5 → **four factors prothrombin > fresh frozen plasma** should be administered before endoscopy.

- **HB for endoscopy 9-10g/dl**

Scanned with CamScanner

In-patient with severe GI bleeding, it is desirable to transfuse blood before the HB reaches 7g/dL to prevent decrease below that level occurring from hemodilution with fluid resuscitation. Furthermore, in actively bleeding patients, platelets are transfused if platelet count is less than 50,000/ mcL (50×10^9/L) and considered if there is impaired platelet function regardless of the platelet count.

Management of Upper GI bleeds due to peptic ulcer

- may present as coffee grounds emesis ,hematemesis , melena or heamatochezia
- emergent upper endoscopy is diagnostic and therapeutic
- **ABC Approach**
- patient who are found to have major endoscopic stigmata of recent haemorrhage can be treated endoscopically using a thermal or mechanical modality, such as a heater probe or endoscopic clip ,combined with injection of dilute adrenaline into the bleeding point (dual therapy). A biologically inert haemostatic mineral powder (TC325, heamospary) can be used as rescue therapy when standard therapy fails.
- Intravenous Proton pump inhibitors (PPI) (80mg bolus injection followed by 8mg/h continuous infusion for 72 hours) should be administered for 3 days after endoscopic therapy in patient whose endoscopic finding are suggestive of a high risk of rebleeding ulcer e.g. an ulcer with active bleeding, visible vessel and adherent clot .
- **IV PPI are associated with** a reduction in rebleeding, transfusion, need for further endoscopic therapy and surgery.
- After initial successful endoscopic treatment of ulcer haemorrhage **IV PPI** reduces the rebleeding rate from 20% to less than 10%.

Complications of peptic ulcer disease

- **gastrointestinal hemorrhage**
- **ulcer perforation→ abdominal CT** for diagnosis→ laparoscopic closure is preferred than open laparotomy
- **Gastric outlet obstruction** →a succussion splash may be heard in epigastrium and nasogastric aspiration will result in evacuation of a large amount of (>200mL) of foul smelling fluid, which establishes the diagnosis. Patients are initially treated with iv fluid, replacement of electrolyte, IV PPI and nasogastric decompression followed by endoscopy to define the nature of the obstruction and to exclude gastric malignancy.

Scanned with CamScanner

Non-cirrhotic portal hypertension

- upper GI bleeding from esophageal varices or gastric varices in patient without cirrhosis
- Causes include extrahepatic portal vein obstruction (portal vein thrombosis often with cavernous transformation,) splenic vein obstruction (due to pancreatitis or pancreatic cancer, presenting as gastric varices without esophageal varices), schistosomiasis, and nodular regenerative hyperplasia(mat be associated with collagen vascular disease , myleoproliferative disorder and drugs like azathioprine, 5-fluorouracil , oaxaliplatin) arterial-portal vein fistula and idiopathic
- other risk factors are OCPs , pregnancy , chronic inflammatory disorder like chronic pancreatitis , injury to the portal venous system (due to surgery)malignancy ,treatment of thrombocytopenia with eltrombopag and inherited or acquired hypercoagulable state
- Clinical features may include abdominal pain, upper GI bleed and ascites in 25% of the cases. apart from splenomegaly , physical finding may be unremarkable

Investigation

- color Doppler ultrasonography is the initial test for portal vein thrombosis
- contrast – enhanced CT or magnetic resonance angiography(MRA) of the portal system is confirmatory
- MRCP →may demonstrate compression of the bile duct by a large portal cavernoma(portal biliopathy)
- CT abdomen→ may show intrabdominal source of infection and hepatic abscess
- endoscopy → for gastric varices
- elastography→ may help distinguish non-cirrhotic portal hypertension from cirrhosis

Treatment

- for isolated acute portal vein thrombosis , anticoagulation particularly with LMWH, unfractionated heparin or thrombolytic therapy (may leads to at least partial recanalization in up to 75% of cases if started within 6 month of thrombosis)
- splenectomy if upper GI bleeding is due to splenic vein thrombosis and for upper GI bleeding due to other causes of Noncirrhotic portal hypertension, band ligation followed by beta-blocker to ↓ portal pressure and followed by TIPS for failure of the endoscopic therapy
- liver transplantation for progressive liver failure

Portal Hypertension

- Normal hepatic venous pressure gradient (difference between the wedged hepatic venous pressure (WHVP) and free hepatic venous pressure) is 5-6 mmHg
- Clinically significant portal hypertension is present when the gradient exceeds 10 mmHg and risk of variceal bleeding increases beyond a gradient of 12 mmHg.

Scanned with CamScanner

- Extrahepatic portal vein obstruction is the usual source of portal hypertension in childhood and adolescence, while cirrhosis causes 90% of cases of portal hypertension in adult in developed countries.

Causes

Pre-hepatic pre-sinusoidal

Portal vein thrombosis due to sepsis (umbilical, portal pyaemia) or procoagulopathy or secondary to cirrhosis and abdominal trauma including surgery

1) **Intrahepatic pre-sinusoidal** schistosomiasis, congenital hepatic fibrosis, drugs vinyl chloride and sarcoidosis.
2) **Sinusoidal** cirrhosis polycystic liver disease nodular regenerative hyperplasia metastatic malignant disease.
3) **Intrahepatic post-sinusoidal** veno –occlusive disease.
4) **post-hepatic –sinusoidal** budd – chiari syndrome

Clinical features

- Clinical features result principally from **portal venous congestion** and **collateral vessel formation.**
- **variceal bleeding**→ due to portal hypertension which commonly arises from esophageal varices within 3-5cm of the gastro-esophageal junction or from gastric varices .rectal bleeding ,that is also result from collateral vessel formation , may be mistaken for hemorrhoid .
- **splenomegaly** is a cardinal finding and a diagnosis of portal hypertension is unusual when splenomegaly cannot be detected clinically or by ultrasound .spleen is rarely enlarged more than 5cm in adult while in children and adolescence there may be marked splenomegaly
- **caput medusae** →collateral vessel visible on the anterior abdominal wall
- **Fetor hepaticus**→this result from portosystemic shunting of blood which allows mercaptans to pass directly to the lungs.
- **Ascites**→ occours as result of renal sodium retention and portal hypertension
- **Cruveihier-Baumgarten syndrome**→ a large umbilical collateral vessel that has a blood flow sufficient to give a venous hum on **auscultation.**

Investigations

- **the diagnosis** is often made **clinically**
- Portal venous pressure measurement are rarely done but can be used to confirm portal hypertension and differentiate sinusoidal and pre-sinusoidal forms.
- **pressure measurement** are made by using a balloon catheter inserted using the transjugular route(via inferior vena cava into a hepatic vein and then hepatic venule) to measure the wedged hepatic venous pressure (WHVP).this is indirect measurement of portal vein pressure .
- **CBC**→ thrombocytopenia is common due to hypersplensim and platelets counts are usually in the range of 100×10^9/L. value below 50×10^9/L are uncommon

Scanned with CamScanner

- **Endoscopy** →it is the most useful investigation to determine whether gastro-esophageal varices are present as result of portal hypertension
- **Ultrasonography** →may show features of portal hypertension such as splenomegaly and collateral vessel. It may sometime indicate the cause of portal hypertension, such as liver disease or portal vein thrombosis.
- **CT/MR angiography** →identify the extent of portal vein clot and are used to identify hepatic vein patency.

Complications of portal hypertension

- variceal bleeding like esophageal, gastric and others
- congestive gastropathy
- hypersplensim
- ascites
- hepatic encephalopathy
- renal failure
- Iron deficiency anemia due to repeated minor bleeds from congestive gastropathy.

Prognosis

- In the presence of portal hypertension, the risk of variceal bleed occurring within 2 years varies from 7% for the small varices up to 30% for large varices.
- The mortality following a variceal bleed has improved to around 15% overall but is still about 45% in those with poor liver function (Child-Pugh C).

Scanned with CamScanner

HEPATITIS C

Summary of European Association for the Study of Liver (EASL)

How will you investigate this patient?

- **HCV serology** by immunoassay (anti-HCV antibodies). this may takes 6-12 weeks to appear in the blood following acute infection
- **PCR for detection** of HCV RNA in serum or plasma (detectable 2-4 weeks after infection) by a sensitive molecular method with a lower limit of detection <15 IU/ ml .when PCR is not available than HCV core antigen should be determined.
- **Liver function tests** .it may be normal (40%) or shows fluctuating serum transaminases between 50 and 200U/L.
- **Molecular analysis,** there are six common viral genotype with variable worldwide distribution. Genotype has no effect on progression of liver disease but does affect response to treatment. in pak, genotype 3 is common while during interferon era genotype 1 was less easy to eradicate.
- **Liver biopsy** serum transaminases levels in hepatitis C are a poor predictor of the degree of liver fibrosis and so liver biopsy may be required to stage the extent of liver damage. The degree of inflammation and fibrosis can be scored histologically by using Metavir system, which scores fibrosis from1-4, the latter equating to cirrhosis. recently, **non-invasive markers**(haptoglobulin, a_2- macroglobulin or combination of hyaluronic acid , procollagen peptide III and tissue inhibitor of metalloproteinase1) and **fibrosis scoring system**(transient elastography also called Fibroscan) have been used routinely ,with biopsy being reserved for cases where these give conflicting result
- **ultrasonography**→ it is good for detection of abnormalities in liver texture but is less effective at identifying diffuse parenchymal disease and lesion that is less than 2cm in diameter
  - chronic hepatitis C develops in up to 85% of patient with acute hepatitis C
  - progression to cirrhosis occours in 20% of affected patients after 20 years

What are the routes of transmission of hepatitis C?

- Intravenous drug misuse (95%)
- unscreened blood products
- Vertical transmission (3% risk)
- needle stick injury (3% risk)
- sharing toothbrushes/razor
- iatrogenic parental transmission(e.g. contaminated vaccination needle)
- sexual transmission
- contaminated surgical equipment

What are the predictors of poor response to treatment?

- obesity
- metabolic syndrome/insulin resistance
- black race

Scanned with CamScanner

- advanced liver fibrosis
- confection with HBV or HIV

Goal of treatment

The goal of therapy is to cure HCV infection in order to

- prevent the complication of HCV-related liver and extrahepatic disease including hepatic necroinflammtion, fibrosis, cirrhosis, decompensation of cirrhosis ,HCC, severe extrahepatic manifestations and death
- improve quality of life and remove stigma
- prevent onward transmission of HCV through treatment as prevention

Pre-therapeutic assessment

- Alcohol consumption and substance abuse should be assessed and quantified with specific counselling given
- extrahepatic manifestation of HCV infection should be identified
- Renal function including creatinine and eGFR ,should be ascertained
- All patient should be tested for past or current HBV infection, for HIV infection and for immunity to HAV
- HBV &HAV vaccination should be proposed to patients who are not immune
- liver disease severity must be assess before therapy
- cirrhosis must be identified as some treatment regimens must be adjusted and post treatment surveillance for HCC is mandatory
- post treatment surveillance for HCC must also be performed in patients with advanced fibrosis (Metavir F3)
- fibrosis stage must initially be assessed by non-invasive methods ,including liver stiffness measurement or serum biomarkers, including APRI &FIB-4 that are not expensive and reliable biomarker panels
- Non-invasive methods should not be used to assess fibrosis stage after therapy and alcoholic –liver disease ,as they are unreliable in this setting
- liver biopsy should be reserved for cases where there is uncertainty or potential additional etiologies
- The contribution of comorbidities to the progression of liver disease must be evaluated and appropriate corrective measures implemented.

Indication of Treatment

- All treatment-naïve and treatment-experienced patients with recently acquired or chronic **HCV** infection must be offered treatment without delay.
- Urgent treatment should must be considered: in patients with significant fibrosis or cirrhosis (METAVIR score F2 F3 or F4), including compensated (Child-Pugh A) and decompensated (Child-Pugh B or C) cirrhosis : in patients with clinically significant extrahepatic manifestation (e.g. Symptomatic vasculitis associated with HCV –related

Scanned with CamScanner

mixed Cryoglobulenemia, HCV immune complex related nephropathy and non-Hodgkin B cell lymphoma): in patients with HCV recurrence after liver transplantation: in patient at risk of a rapid evolution of liver disease because of concurrent comorbidities(non-liver solid organ or stem cell transplant recipients,HBV and HIV confection and diabetes); and in individuals at risk of transmitting HCV(PWIDs, men have sex with men with high-risks sexual practices, women of childbearing age who wish to get pregnant ,patients on haemodialysis, incarcerated individuals)

- treatment is generally not recommended in patients with limited life expectancy due to non-liver related comorbidities)

Contraindications of Treatment

- there are few contraindications to current direct –acting antivirals(DAA) base treatment

1) the concurrent use of certain cytochrome p450/P-Ggp-inducing agents(such as carbamazepine ,phenytoin and phenobarbital) contraindicates all HCV DAA regimen if they cannot be switched to others medications ,due to the risk of significantly reduced concentrations of HCV DDAs(A1)
2) Treatment regimens consisting of an HCV protease inhibitor such as grazoprevir, glecaprevir or voxilaprevir are contraindicated in patients with decompensated (Child Pugh B&C) cirrhosis and in-patient with previous episode of decompensation.

Direct-acting antiviral agents for HCV infection

Agent	Genotype(s)	Dose[2]	Comment
NS3/4A Protease inhibitors			
Glecaprevir	1-6	300 mg orally once daily	Used in combination with pibrentasvir with or without ribavirin
Grazoprevir	1and4	100mg orally once daily	Used in combination with elbasvir[4]
Paritaprevir	1and 4	150mg orally one daily	Used in combination with ombitasvir and dasabuvir;ritonavir (100mg) boosted5; for genotype 1b with cirrhosis and genotype 1a, used with ribavirin. used in combination with ombitasvir, ritonavir boosting, and ribavirin for genotype 4[6]
Simeprevir	1and 4	150 mg orally once daily	Used in combination with sofosbuvir
Voxilaprevir	1-6	100mg orally once daily	Used in combination with sofosbuvir and velpatasvir
NS5A inhibitors			
Daclatasvir	1-6	60mg orally once daily	Used in combination with sofosbuvir (genotype1-6 with or without ribavirin depending on presence of cirrhosis) or with asunaprevir
Elbasvir	1 and 4	50 mg once daily	Used in combination with grazoprevir
Ledipasvir	1-4-6	90mg orally once daily	Used in combination with sofosbuvir[9]

Scanned with CamScanner

Ombitasvir	1and 4	25 mg orally once daily	Used in combination with paritaprevir (ritonavir boosted) with or without dasabuvir and with or without ribavirin as per paritaprevir above
Pibrentasvir	1-6	120 mg orally once daily	Used in combination with glecaprevir with or without ribavirin
Velpatasvir	1-6	100 mg orally once daily	Used in combination with sofosbuvir,[10] may be used with sofosbuvir and voxilaprevir
NS5B Nucleos (t)ide polymerase inhibitor			
Sofosbuvir	1-6	400mg orally once daily	Used in combination with ribavirin (genotypes 2 and 3) or with Simeprevir (genotypes 1 and 4) or with daclatasvir (all genotypes)or with ledipasvir (genotypes 1,3 and 4)or with velpatasvir (all genotypes)or with velpatasvir and voxilaprevir (all genotypes)
NS5B Non-Nucleos(t)ide polymerase inhibitor			
Dasabuvir	1 and 4	250mg orally twice daily	Used in combination with paritaprevir (ritonavir boosted and ombitasvir with or without ribavirin as per paritaprevir above

FDA – Approved Oral Direct –Acting Antiviral (DAA) Treatment Regimens For HCV INFECTION		
Regimen	Indication	Duration of treatment in Non-cirrhotic treatment Naïve patients (weeks)
Glecaprevir and pibrentasvir	Genotypes 1-6 and DAA-experienced genotype 1	8
Sofosbuvir and velpatasvir	Genotypes 1-6 and DAA experienced genotypes 1 band 2	12
Sofosbuvir, velpatasvir and voxilaprevir	DAA experienced genotypes 1-6	-

Treatment regimens of chronic hepatitis C

Standard therapy for HCV infection from the late 90s to the early 2010s was a combination of peginterferon plus ribavirin. The sustained virologic response rates SVR (see next) for this regimen were 70-80% for genotype 2 &3 and 45% for genotype 1 .since 2011, new classes of direct-acting antiviral agents(DAAs) have been developed .initially ,DAAs were added to interferon-ribavirin based regimens : more recently ,however , combination of DAAs have increasingly been used in interferon –free regimens .

Pan-genotypic HCV drug regimens

- These regimens can be used to treat individuals without identifying their HCV genotype and subtype .However, it is still recommended to determine the HCV genotype and subtype where

Scanned with CamScanner

such determination is available and does not limit access to care, to identify patients who may benefit from treatment tailoring.

1) **treatment-naïve patients without cirrhosis or with compensated (Child-Pugh A) cirrhosis and treatment experienced patients (patient who were previously treated for HCV with any available regimen) without cirrhosis should be treated without testing genotype /subtype with either**

- the fixed –dose combination of sofosbuvir (400mg) and velpatasvir (100mg) for 12 weeks (tab velpaget 400/100mg)
- The fixed dose combination of glecaprevir (300mg) and fibrentasvir (120mg) for 8 weeks. patient is advised to take 3 tab containing 100mg of glecaprevir (100mg×3) and 40mg of fibrentasvir (40mg×3) once daily with food.

2) **treatment –experienced patients with compensated (child-Pugh A) cirrhosis should be treated without testing genotype /subtype with either**

- the fixed –dose combination of sofosbuvir (400mg) and velpatasvir (100mg) for 12 weeks (tab velpaget 400/100mg)
- The fixed dose combination of glecaprevir (300mg) and fibrentasvir (120mg) for 12weeks. patient is advised to take 3 tab containing 100mg of glecaprevir (100mg×3) and 40mg of fibrentasvir (40mg×3) once daily with food.
- in region where the IFN (interferon)-free ,ribavirin-free optioned mentioned above are not available or not affordable , the pangenotypic combination of sofosbuvir 400mg and Daclatasvir 60 mg is safe , highly effective and affordable.(tab Daclaget 60mg and tab Sofiget 400mg for 12 weeks for non-cirrhotic and 23 week for cirrhotic)
- Given the high SVR expected with these regimens across all group of patients if adherent, testing for SVR can be omitted(except patient with high-risk behaviors and risk of reinfection who require SVR testing 12 weeks after the end of treatment and then yearly whenever possible)

3) **HCV positive patients with decompensated(child-Pugh B&C) cirrhosis with or without an indication for liver transplantation**

- Patients with decompensated (Child-Pugh B&C) cirrhosis without HCC ,awaiting liver transplantation with a MELD score of 18-20 should be transplanted first and HCV treatment should be started after transplantation
- Patients with decompensated (Child-Pugh B&C) cirrhosis without HCC, awaiting liver transplantation with a MELD score of <18-20 should be treated first for HCV before transplantation.
- If the waiting time for transplant is more than 6 months , patients with decompensated(Child-Pugh B&C) cirrhosis without HCC , awaiting liver transplantation with a MELD score > 18-20 should be treated before transplantation
- Patients with decompensated((Child-Pugh B&C) cirrhosis not on the waiting list for liver transplantation list and without concomitant comorbidities that could impact their survival should be treated urgently

Scanned with CamScanner

- Patients with decompensated ((Child-Pugh B&C) cirrhosis with an indication of treatment should be treated with the fixed –dose combination of sofosbuvir, velpatasvir and weight based ribavirin for 12 weeks.
    - weight > 75mg/kg ,1200mg ribavirin OD
    - weight <75mg/kg, 1000mg ribavirin OD
- Ribavirin should be started at the dose of 600mg daily and subsequently dose adjusted depending on tolerance
    - if Hb drops to ≤ 10 g/L ↓ dose of ribavirin
    - if Hb drops to ≤ 8.5g /L stop ribavirin
- Patients with decompensated ((Child-Pugh B&C) cirrhosis with an indication of treatment with contraindication to ribavirin, or poor tolerance to ribavirin, should be treated with the fixed –dose combination of sofosbuvir and velpatasvir for 24 weeks without ribavirin

4) HCV treatment in patients with HCC

- Patients without cirrhosis or with compensated cirrhosis (child –Pugh A) with HCC who are eligible for potentially curative therapy with liver resection or ablation should defer DAA therapy until treatment is completed
- Patients with HCC awaiting liver transplantation with an HCV infection , the timing of antiviral treatment (prior or post-transplant) should not interfere with the management of the patient on the waiting list and must be decided on a case –by-case basis through a multidisciplinary discussion
- patients with HCC awaiting liver transplantation with a long waiting time , the HCV treatment should be started before the liver transplantation (in order to reduce waiting list dropouts due to tumor progression)
- Patients with HCC without cirrhosis or with compensated (Child-Pugh A) cirrhosis awaiting liver transplantation should be treated for their HCV infection, prior to or after liver transplantation, as per recommendations.

5) HCV treatment in patients with treated HCC without an indication for liver transplantation

- Patient with complete response to HCC therapy should be treated for chronic hepatitis C according to the general recommendation in-patient without HCC.
- Patients with complete response to HCC therapy who achieve SVR have a continued risk of HCC recurrence and require indefinite post –SVR HCC surveillance by means of ultrasonography every 6 monthly.
- Patient palliated for HCC may be treated for HCV depending on the overall prognosis and potential benefits.

6) Treatment of chronic hepatitis C in patient with renal impairment , including patients on hemodialysis

- Chronic HCV patients with mild to moderate renal impairment (eGFR >30 ml/min/1.73m^2) and those with end stage renal disease on hemodialysis, should be treated for their HCV

Scanned with CamScanner

infection according to the general recommendation e.g. no need for dose adjustment of HCV DAAs.

- The fixed –dose combination of glecaprevir and pibrentasvir (pan-genotype) or grazoprevir& Elbasvir (for genotype 1b) are the preferred regimens in patients with severe renal impairment (eGFR < 30 ml/min/1.73m^2) and in those with end stage renal disease requiring hemodialysis.
- patients with decompensated(child-Pugh B&C) cirrhosis and mild to moderate renal impairment (eGFR >30 ml/min/1.73m^2) should be treated with the fixed –dose combination of sofosbuvir and velpatasvir along with ribavirin for 12 weeks
- patients with decompensated(child-Pugh B&C) cirrhosis and severe renal impairment (eGFR <30 ml/min/1.73m^2) should be treated with the fixed –dose combination of sofosbuvir and velpatasvir along without ribavirin for 24 weeks

Protease inhibitors are contraindicated with decompensated (child-Pugh B &C) and previous episode of decompensation.

- The risk vs. benefits of treating patients with end-stage renal disease and an indication for kidney transplantation before or after renal transplantation require individuals' assessment.

➢ HCV pattern of kidney injury

- membranoproliferative GN(type 1) > membranous GN

7) treatment of chronic hepatitis C inpatients with immune complex- mediated manifestation of HCV infection

- mixed Cryoglobulenemia and renal disease associated with chronic HCV infections should be treated with pangenotypic DAA combination, according to the general recommendation
- careful monitoring for adverse events is mandatory when treating mixed Cryoglobulenemia and renal disease associated with chronic HCV infection with pangenotypic DAA combination
- an acute flare of Cryoglobulenemia may be first require treatment with rituximab, cyclophosphamide plus methylprednisolone or plasma exchange.
- the indication for rituximab in HCV-related renal disease must be discussed by multidisciplinary team
- HCV –associated lymphoma should be treated with pangenotypic DAA regimens according to the general recommendation, in combination with specific chemotherapy taking into account possible drug –drug interaction.

8) treatment of chronic hepatitis C in pregnant women

- HCV treatment during pregnancy is not recommended in the absence of safety and efficacy data
- treatment can be considered during pregnancy, or in the case of accidental conception during treatment, only on a case basis after a thorough discussion with the patient about the potential risks and benefits and in a joined up approach with hepatology and obstetric services
- breastfeeding is not contraindicated in women with HCV, expect in the case of bleeding or cracked nipples for which specialist advice should be sought

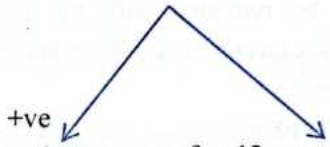
9) Treatment of chronic hepatitis C in adolescents

Scanned with CamScanner

- all children born to HCV infected women should be tested for HCV infection from the age of 18 months
- adolescents aged 12-17 years who are treatment naïve or treatment experienced, without cirrhosis or with compensated (child-Pugh) cirrhosis, should be treated according to the general recommendations in adult patients with either:(i) the fixed dose combination of sofosbuvir (400 mg) and velpatasvir (100 mg)in a single tablet administered once daily ; or (ii) the fixed dose combination of glecaprevir (300 mg) and pibrentasvir (120 mg)in 3 tablets (100 mg/40mg)administered once daily with food

➢ **Baby born to HCV+ mothers**

Anti HCV antibody of the baby at birth or at 18 months



- If positive then PCR at age of 3 years and treat at or after 12 years of age or when weight is > 35kg.

10) treatment of chronic hepatitis C in patients with HBV co-infection

- patients coinfection with HCV and HBV should be tested for HIV if their HIV status is unknown
- patients coinfected with HCV and HBV should be treated with the same anti HCV regimens, following the same rules as HCV-mono infected patients
- there is a potential risk of HBV reactivation during or after HCV clearance, but the risk is unpredictable
- patients coinfected with HCV and HBV fulfilling the standard criteria for HBV treatment should receive nuleoside/nucleotide analogue treatment
- patients who are HBs antigen positive should receive nucleoside /nucleotide analogue prophylaxis at least until week 12 post anti HCV therapy and be monitored monthly if HBV treatment is stopped
- Patients who are HBs antigen negative but anti HBc antibody positive, serum ALT levels should be monitored monthly to detect possible reactivation.

11) HCV patients co-infected with HIV

- the same IFN-free ,ribavirin –free treatments regimens should be used in HIV-coinfected patients as in patients without HIV infection , because the virologic result of the treatment are identical , however , treatment alteration or dose adjustment should be performed in case of interactions with antiretroviral drugs
- moreover, in person coinfected with HCV and HIV ,long –term liver disease-related mortality increases as HIV infection –related mortality is reduced by antiretroviral therapy

Scanned with CamScanner

12) Retreatment of Direct acting antiviral (DAAs) Failure

- HCV resistance testing prior to retreatment in patients who failed after any of the DAA-containing treatment regimens is useful to guide retreatment by probabilities of response , according to the resistance profile observed
- patients without cirrhosis or with compensated cirrhosis (Child-Pugh)A who failed after a DAA (protease inhibitor and /or NS5A) –containing regimen should be retreated with the fixed –dose combination of sofosbuvir , velpatasvir and voxilaprevir for 12 weeks
- patients without cirrhosis or with compensated cirrhosis (Child-Pugh)A who failed after a DAA (protease inhibitor and /or NS5A) –containing regimen and have predictors of lower response (advanced liver disease , multiple courses of DAA-based treatment, complex NS5A RAS profile) can be retreated with the combination of sofosbuvir plus fixed dose combination of glecaprevir and fibrentasvir for 12 weeks , based on individual multidisciplinary decision

Endpoint of HCV therapy

- the endpoint of therapy is undetectable HCV RNA in serum or plasma by an assay with lower limit of detection < 15 IU/ml, 12 weeks (SVR12) or 24 weeks (SVR24) after the end of therapy
- undetectable HCV core antigen in serum or plasma 12 weeks (SVR12) OR 24 weeks (SVR 24) after the end of therapy can be used as an alternative endpoint of therapy in patients with detectable HCV core antigen prior to therapy
- undetectable HCV core antigen in serum or plasma 12 weeks (SVR12) OR 24 weeks (SVR 24) after the end of treatment using a qualitative HCV RNA assay with a lower limit of detection <1000 IU/ml cab be used as an alternative endpoint of therapy where sensitive HCV RNA assays are not available and/ or not affordable
- in patient with advanced fibrosis (METAVIR score F3) and cirrhosis (METAVIR F4) , surveillance for HCC must be continued because an SVR will reduce ,but not abolish , the risk of HCC

Viral response

1) Rapid Viral Response (RVR)
   PCR negative after one –month of treatment
2) Early viral Response (EVR)
   When PCR negative at the end of 3months of treatment e.g. on the last day of treatment course
3) Sustained Viral Response (SVR)
   PCR negative 3-6 months (12 or 24 weeks) after treatment

Post-Treatment Follow-Up of Patients Who Achieve an SVR

- patient with no to moderate fibrosis (METAVIR score F0-F1) with SVR and no on-going risk of behaviour should be discharged, provided that they have no others comorbidities

Scanned with CamScanner

- patient with advanced fibrosis (F3) or cirrhosis (F4) with SVR should undergo surveillance for HCC every 6 months by means of ultrasonography, because the risk of de novo or incident of HCC is reduced but not abolished by SVR
- in patients with cirrhosis , surveillance for esophageal varices by endoscopy should be performed if varices were present at pre-treatment endoscopy , or if the platelets count falls below 150,000 and elastography increases to more than 20 Kpa(A1)
- The risk of reinfection should be explained to positively modify risk behaviour in at-risk population
- Following SVR , monitoring for HCV reinfection through bi-annual or , at least annual HCV RNA assessment should be undertaken in people who inject drugs(PWID) or men have sex with men with on-going risk behaviors
- retreatment should be offered without stigma or delay to those patients who are re-infected

Prognosis

- chronic hepatitis C often lead to cirrhosis and hepatocellular carcinoma after decades
- the overall mortality rate in patients with transfusion –associated hepatitis C may be no different from that of an age –matched control population
- Mortality or transplantation rates rise to 5% per year once cirrhosis develops.
- there is some evidence that HCV genotype Ib is associated with a higher risk of hepatocellular carcinoma than other genotypes
- antiviral therapy has a beneficial effect on mortality , cardiovascular events ,type 2 diabetes and quality of life , is cost effective , appears to retard and even reverse fibrosis and reduce (but does not eliminate)the risk of decompensated cirrhosis and hepatocellular carcinoma in responder with advanced fibrosis
- HCV infection appears to be associated with increased cardiovascular mortality , especially in person with diabetes and hypertension
- statin has been reported to be associated with improved virologic response to anti-viral therapy and ↓ progression of liver fibrosis and frequency of hepatocellular carcinoma.

TREATMENT OF ACUTE HEPATITIS C

- the term "recently acquired " hepatitis C is more appropriate than acute hepatitis C
- recently acquire de novo HCV infection is defined by the presence of anti-HCV antibodies ,HCV RNA and /or HCV core antigen that were not detectable in previous samples up to 12 months
- if such historical sample are unavailable the diagnosis of recently acquired hepatitis C IS based on the presence of HCV RNA OR HCV core antigen, in or the presence or absence of anti HCV antibodies associated with a 3-fold or greater rise in ALT levels above

Scanned with CamScanner

baseline in an individual who had a risk behaviour in the preceding 6 months and in the absence of other causes of such liver injury

- recently acquired HCV reinfection uses the same criteria following spontaneous or DAA induced viral clearance
- patients with recently acquired de novo hepatitis C should be treated with the combination of sofosbuvir and velpatasvir or with the combination of glecaprevir and pibrentasvir for 8 weeks
- SVR should be assessed 12 and 24 weeks after treatment , because late relapses have been reported(B2)
- there is indication for antiviral therapy as post exposure prophylaxis in the absences of documented HCV transmission

Treatment monitoring

- HCV RNA or HCV core antigen detection should be performed at week 12(SVR12) OR 24(SVR24) post treatment to assess whether treatment has been successful
- Given the high SVR rates expected with pan genotypic DAA based regimens, checking SVR is dispensable , expect in patients with high risk behaviors and in patients at risk of reinfection
- the patients receiving a DAA containing regimen should be assessed for clinical side effects at each visit
- ALT levels should be assessed at least at baseline and at 12(or 24) weeks post treatment, and in case of suggestive symptoms
- Renal function should be checked monthly in patients with reduced e GFR
- when possible, an interacting co- medication should be stopped for the duration of HCV treatment, or the interacting co medication should be switched to an alternative drug with less interaction potential
- Treatment should be stopped in case of severs adverse events or in case of Alt flare > times the upper limit of normal values
- in patients with decompensated (child-Pugh B or C) cirrhosis who need ribavirin, ribavirin administration should be stopped if the hemoglobin level drops below 8.5g/**dl**

Scanned with CamScanner

VIVA OF HEPATITIS B

interpretation	HBsAg	Anti-HBs	Anti-HBc	HbeAg	Anti-HBe
Acute hepatitis B	+	–	IgM	+	–
Chronic hepatitis B with active viral replication	+	–	IgG[a]	+	–
Inactive HBV carrier state low HBV DNA level) or HbeAg-negative chronic hepatitis B with active replication(high HBV DNA level)	+	–	IgG	–	+
Chronic hepatitis B with heterotypic anti-HBs (about 10% of cases)	+	+	IgG	+ or –	+or–
Acute hepatitis B	–	–	IgM	+ or –	–
Recovery from hepatitis B immunity	–	+	IgG	–	+or–
Vaccination (immunity)	–	+	–	–	–
False-positive, less commonly, infection in remote past	–	–	igG	–	–

a→ low levels of IgM anti-HBc may also be detected

- hepatitis B is one of the most common causes of chronic liver disease worldwide
- Hepatitis B may causes an active viral hepatitis ;however , acute infection is often asymptomatic , particularly when acquired at birth
- many individuals with chronic hepatitis B is also asymptomatic
- the risk of progression to chronic liver disease depends on the source and timing of the infection
- vertical transmission in perinatal period is the most common cause of infection worldwide and carries the highest risk of on-going chronic infection

Mode of Transmission

1) **Horizontal transmission** (10%)
   - iv drug abuser
   - infected unscreened blood product
   - tattoos/acupunctures needles
   - sexual transmission
   - close living quarters /playground play as toddlers (may contribute to higher rate of horizontal transmission in Africa)
2) **Vertical transmission (90%)**
   - Hepatitis B surface antigen (HbsAg) –positive mother

How will you investigate this patient?

- HBV-DNA can be measured by PCR in the blood; viral loads are usually in excess of 10^5copies /mL in the presence of active viral replication, as indicated by the presence of e antigen. in contrast, in individuals with low viral replication, who are HbsAg negative and anti-HBe-positive, viral loads are less than 10^5copies /mL .the exception is in patient who have a mutation in the pre-core protein, which means they cannot secrete e antigen into serum .such individuals will be anti-Hbe-positive but have a high viral load and often

Scanned with CamScanner

evidence of chronic hepatitis and patients affected area classified as having e antigen – negative chronic hepatitis. They respond differently to antiviral drugs from those with classic e antigen –positive chronic hepatitis. Additionally, measurement of viral load is important in monitoring anti-viral therapy and identifying pre-core mutant. Specific genotype (A-H) can also be identified by PCR.

- HbsAg .it is indicator of active infection and negative HbsAg makes infection very unlikely (do hepatitis B core IgM it signify recent evidence of infection) HbsAg appears in the blood late in the incubation period but before the prodromal phase of acute type B hepatitis: it may be present for few a few days only, disappearing even before jaundice has resolved, but usually last for 3-4 weeks and can persist for up to 5 months. The persistence of HbsAg for longer than 6 months indicates chronic infection. antibody to HbsAg (Anti-HBs) usually appears after about 3-6 months and persist for many years or perhaps permanently .anti-HBs implies either a previous infection , in which case anti-HBc is usually also present , or previous vaccination , in which case anti-HBc is not present
- Hepatitis core antigen (HbcAg) the HbcAg is not found in the blood ,but antibody to it (anti-HBc) appears early in the illness and rapidly reaches a high titer that subsides gradually but then persist.anti-HBc (IgM) can sometime reveal an acute HBV infection when the HbsAg has disappeared and before anti-HBs has developed
- Hepatitis B e antigen (HbeAg).it is an indicator of viral replication .in acute hepatitis B it may appear only transiently at the outset of the illness .HbeAg reflects active replication of the virus in the liver. Chronic HBV infection is marked by the presence of HbsAg and anti-HBc (IgG) in the blood .usually, HbeAg or anti-HBe is also present. the absence of HbeAg usually implies low viral replication : the exception is HbcAg –negative chronic hepatitis B (also called " pre-core mutant" infection) in which high levels of viral replication ,serum HBV-DNA and hepatic necroinflammtion are seen , despite negative HbeAg .

Initial evaluation of patients with chronic HBV infection

- The initial assessment of patients with chronic HBV infection should include a complete history, a thorough physical examination, and assessment of liver disease activity severity and markers of HBV infection.
- HBV genotype is not necessary in the initial evaluation, although it may be useful for Immune tolerant Phase
- all first-degree relatives, sexual partners of patients with chronic HBV infection should be advised to be tested for HBV serological markers (HbsAg, Anti-HBs, anti-HBc) and to be vaccinated if they are negative for these markers.
- The assessment of the severity of liver disease is important to identify patients for treatment and HCC surveillance. It is based on a physical examination and biochemical parameter *([AST, ALT, and GGT, alkaline* phosphatase, bilirubin, and serum albumin and gamma globulins, full blood count and prothrombin time).

Scanned with CamScanner

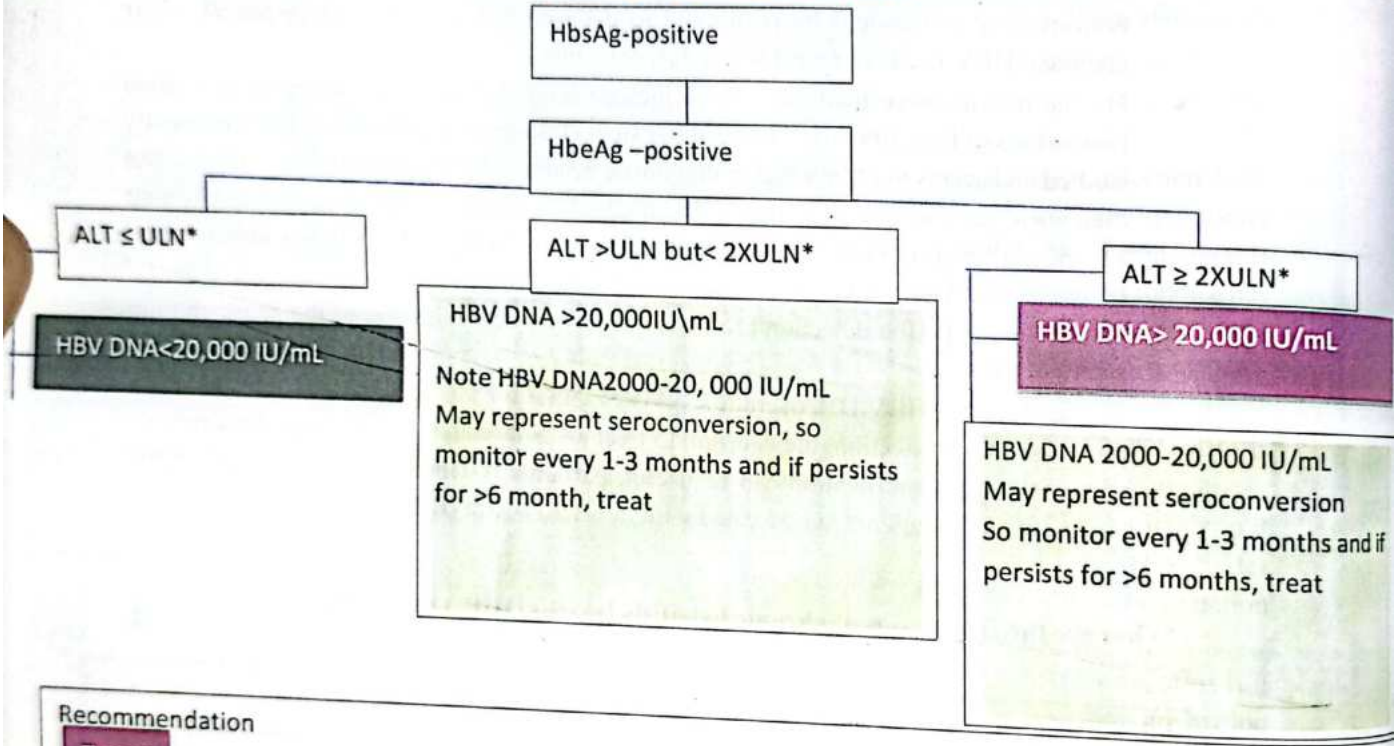
- An abdominal hepatic ultrasound is recommended in all patients. A liver biopsy or a non-invasive test should be performed to determine disease activity in-patient where chemical HBV markers reveal inconclusive results.
- On the non-invasive methods, which include liver stiffness measurements and serum biomarkers of liver fibrosis, the use of transient elastography (Fibroscan) has been mostly studied and seems to offer a higher diagnostic accuracy for the detection of cirrhosis. The diagnostic accuracy of all non-invasive methods is better at excluding than confirming advanced fibrosis or cirrhosis. The result of transient elastography may be confounded by severe inflammation associated with high ALT levels.
- HbeAg and anti-Hbe detection are essential for the determination of the phase chronic HBV infection.
- Measurement of HBV DNA serum level is essential for the diagnosis, establishment for the phase of the infection, the decision to treat and subsequent monitoring of patients.
- Serum HbsAg quantification can be useful, particularly HbeAg-negative chronic HBV infection and in patients to be treated with interferon-Alfa (IFNa)

What are the five phases of chronic hepatitis B virus (HBV) infection?

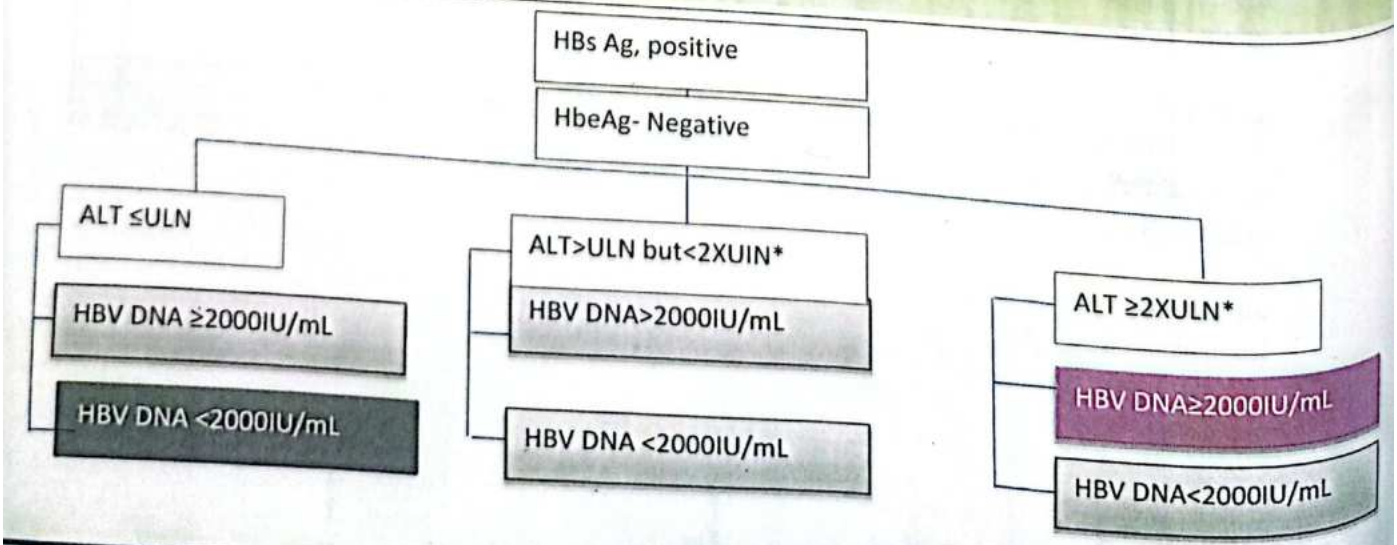
Phase	HBsAg	HBeAg	Anti-Hbe AB	Viral load	ALT
immune-tolerant phase	+	+	—	+++	Normal\low
immune-reactive HbeAg- positive chronic hepatitis phase	+	+	—	++	Raised
Inactive carrier phase	+	—	+	—\+	Normal
HbeAg-negative chronic hepatitis B	+	—	+	+\++	Raised \fluctuating
HBsAg-negative phase	—	—	+	—\±	Normal

Scanned with CamScanner

INDICATION OF TREATMENT


HbsAg-positive
HbeAg –positive
ALT ≤ ULN*
HBV DNA<20,000 IU/mL
ALT >ULN but< 2XULN*
HBV DNA >20,000IU\mL
Note HBV DNA2000-20, 000 IU/mL
May represent seroconversion, so monitor every 1-3 months and if persists for >6 month, treat
ALT ≥ 2XULN*
HBV DNA> 20,000 IU/mL
HBV DNA 2000-20,000 IU/mL
May represent seroconversion
So monitor every 1-3 months and if persists for >6 months, treat

Recommendation	
Treat	
Do not treat. Monitor with ALT and HBV DNA levels every 3.6 months and HbeAg every 6.12 months..	
Exclude other causes of ALT elevation and assess disease severity with non –invasive tests and/or liver biopsy .if staging indicates ≥F2 or ≥A3, treat. If other causes of ALT >ULN excluded and elevation persist, treat, especially if age > 40	



Scanned with CamScanner

Recommendations:

Treat

Do not treat, monitor with ALT and HBV DNA levels 3.6 months and HbsAg

If ALT ≤ULN, monitor ALT and HBV DNA every 3 months for 1 year, then every 6 months.

If ALT elevated, exclude other causes of ALT elevation and assess disease severity with non-innovative tests and /or liver biopsy.Ifstaging indicates ≥F2 or ≥A3, treat: if persistent ALT >ULN, with HBV DNA ≥2000 IU/mL, treat, especially if age>40.

Monitoring of patients

- all patients treated with nucleotide /nucleoside analogue (NA) should be followed with periodical evaluation including ALT and HBV DNA
- patients at risk of renal disease treated with any NA and all patients irrespective of renal risk treated with tenofovir disoproxil fumarate(TDF) should undergo periodic renal monitoring GFR estimation and serum phosphate levels
- patients on TDF at risk of development and /or with underlying renal or bone should be considered for a switch to entacavir (ETV) or tenofovir alafenamide(TAF) depending on previous lamivudine (LAM)exposure

Available NA analogs

1) entacavir
2) tenofovir
3) lamivudine
4) adefovir and telbivudine

They all differ in efficacy and rates of resistance, however, in HbeAg-positive patients; they all achieve an HbeAg to anti-Hbe seroconversion rates of 20% at 1 year and with higher rates, after more prolong therapy .they preferred first line regimen **is entacavir and tenofovir.**

1) **Entacavir daily** dose 0.5mg for lamivudine sensitive and 1mg daily for lamivudine resistant patient

- It causes suppression of HBV DNA in serum occours in nearly all treated patients, and histologic improvement is observed in 70% of patients.

SE: tenofovir is associated with lactic acidosis in patients with decompensated cirrhosis

2) **tenofovir**

A) tenofovir disoproxil fumarate**(TDF) 300mg daily**
TDF is equally effective and is used as a first line agent or when resistance to a nucleoside analogue has developed
SE: long-term TDF may leads to elevated creatinine and reduced serum phosphate (Fanconi-like syndrome) that is reversible

B) Tenofovir alafenamide **(TAF) 25mg**

Scanned with CamScanner

It is new alternative formulation of tenofovir that is associated with **lower rate of renal and bone toxicity** than tenofovir disoproxil fumarate

3) **Lamivudine 100mg daily**

The first available nucleoside analogue, however, it is no longer considered first line agent

4) **Telbivudine 600mg daily**

It is more potent than either lamivudine or adefovir but like them is associated with resistance .it may cause elevated creatine Kinase

5) **Adefovir dipivoxil**

It has activity against wild type and lamivudine resistant HBV but in a standard dose of daily, it is the least of the oral potent agents against HBV and therefore rarely used.

6) **peginterferon alfa-2a**

it is alternative to the oral agent's .a dose of 180mcg SC /week for 48 weeks leads to sustained normalization of aminotransferase levels , disappearance of HbeAg and HBV DNA from serum and appearance of anti-Hbe in up to 40% of treated patients and result in improved survival. It is more effective in those infected with HBV genotype A than with other genotype .patient with HbeAg –negative chronic hepatitis B have a response rate of 60% after 48 weeks of therapy but the response may not be durable once interferon is stopped .

Long-term outcome during NA therapy

- HCC surveillance should be ensured in all those who are under effective long-term NA therapy
- HCC surveillance is mandatory for all patients with cirrhosis as well as those with moderate or high HCC risk scores at the onset of therapy

When to stop treatment

- NA should be discontinued after confirmed HbsAg loss , with or without anti-HBs seroconversion
- NA can be discontinued in non-cirrhotic HbeAg-positive chronic hepatitis B patients who archive stable HbeAg seroconversion and undetectable HBV DNA and who complete at least 12 months of consolidation therapy .Close post-NA monitoring is strongly warranted
- Discontinuation of NA in selected non-cirrhotic HbeAg –negative patients who have achieve long-term (3years) virological suppression under NAs may be considered if close post-NA monitoring can be taken

Endpoints of therapy

- the induction of long term suppression of HBV DNA levels represents the main endpoint of all current treatment strategies
- the induction of HbeAg loss with or without anti HBE seroconversion in HbeAg positive chronic hepatitis patients is a valuable endpoint as it often represent a partial immune control of the chronic HBV infection

Scanned with CamScanner

- a biochemical response defined as ALT normalisation should be considered as an additional endpoint which is achieved in most patients with long term suppression of HBV replication
- HbsAg loss with or without anti HBs seroconversion is an optimal endpoint as it indicates profound suppression of HBV replication and viral protein expression

TREATMENT OF CHRONIC HEPATITIS B IN DECOMPENSATED CIRRHOTIC PATIENT

- Nucleoside and nucleotide analogue are well tolerated even in patients with decompensated cirrhosis
- treatment threshold for such group of patients may be an HBV DNA level less than 10^4 copies /mL
- therapy should be continued indefinitely
- PegIFNa(interferon) is contraindicated in decompensated patients
- such patient should be closely monitored for tolerability of the drugs and rare adverse effects like lactic acidosis or kidney dysfunction

Treatment of HDV Co-infected patients

- **Peginterferon alfa-2b** 1.5mcg/kg/week for at least 48 weeks is the current treatment of choice in HDV HBV co infected patients with compensated liver disease
- this leads to normalization of aminotransferase levels, histologic improvement and elimination of HDV RNA from serum in 20-50% of the patients
- nucleoside and nucleotide are not effective in HDV treatment
- PegIFNa treatment can be continued until week 48 irrespective of on treatment response pattern if well tolerated

Treatment of HCV CO infected patients

- Treatment of HCV with direct acting antivirals (DAAs) may cause reactivation of HBV
- Patients fulfilling the standard criteria for HBV treatment Should receive NA treatment
- HbsAg positive patients undergoing DAA therapy should be considered for concomitant NA prophylaxis until week 12 post DAA and monitored closely
- HbsAg negative anti HBs positives patients undergoing DAA should be monitored and tested for HBV reactivation in case of ALT elevation

Treatment of HIV co-Infected Patients

- co-infection should be managed by specialist with expertise in this area
- All HIV positive patients with HBV co infection should start antiretroviral therapy irrespective of CD4 cell count
- patients infected with HBV &HIV, antiretroviral therapy (TDF or TAF based ART regimen plus lamivudine or emtricitabine) is recommended when treatment of HIV infection is indicated

Treatment of pregnant woman infected with chronic hepatitis B

Scanned with CamScanner

- screening for HbsAg in the first trimester of pregnancy is strongly recommended
- in a women of childbearing age without advanced fibrosis who plans a pregnancy in the near future it may be prudent to delay therapy until the child is born
- in all pregnant women with high HBV DNA levels greater than 200000 IU/ML or HbsAg level > 4 log 10 IU/ML , previous child infected with HBV and advanced fibrosis should be offer, antiviral prophylaxis with TDF should start at week 24 -28 of pregnancy and continue for up to 12 weeks after delivery.

- pregnant women with CHB and advanced fibrosis or cirrhosis therapy with TDF is recommended
- in pregnant women already on NA therapy TDF should be continued while emtricitabine (ETV) or other NA should be switched to TDF
- normal vaginal delivery is recommended
- Breast feeding is not contraindicated in HbsAg positive untreated women or on TDF based treatment or prophylaxis
- Baby born to chronic hepatitis B patient should be given IV G and 1st dose Hep B vaccine followed by standard vaccination.
- screening of sexual partner should be done
- follow-up at 1, 2 and 6months post-partum is recommended for hepatitis B flare (ALT and PCR)

Acute Hepatitis B

- More than 95-95% of adults with acute HBV hepatitis do not require specific treatment because they will fully recover spontaneously
- 5-10 develops chronic infection that continue for life
- there is no evidence that antiviral therapy reduces the severity or duration of acute hepatitis
- acute liver failure occur in less than 1%
- Only patients with severe acute hepatitis B characterized by coagulopathy or protracted course should be treated with NA and considered for liver transplantation

Vaccination of hepatitis

- vaccine name **Engerix ™ -B**
- 0 , 1 , 6 months IM

Accelerated vaccine regimen

- vaccine name **HEPLISAV-B**
- 0 , 1 months IM

Methods of Liver Biopsy

A) invasive – liver biopsy

- trucut biopsy needle

Scanned with CamScanner

- vim Silverman needle
- manghini needle

B) non –invasive (equivalent to invasive liver biopsy

- Fib-4
- APRI index
- fibro scan /elastography
- fibro test

Needles stick injury transmission risk

- HIV→0.3%(percutaneous exposure) and 0.09 % after mucous membrane exposure
- HCV→ 1.8% (but range is 0-7%)
- HBV→20-30% but depend on
    - if the source is HbsAg and HbeAg positive than risk of transmission is →37-62%
    - if the source is HbsAg and HbeAg negative than risk of transmission is →23%-37%

Scanned with CamScanner

APPROACH TO JAUNDICE

P/C

Yellow discoloration of sclera 10 days

HOPI (&ODPARA)

My patient presented with yellow discoloration of sclera for the last 10 days that was sudden in onset, progressive in nature .initially, patient, s daughter noticed the yellow tinge that later on, involved the most of the body. The yellowish discoloration is not aggravated by fasting and relived by medication. It is associated with … However, patient denied HX of

DDs

A) Pre-hepatic causes of jaundice

- patient denied family Hx of paleness of complexion ,repeated blood transfusion and heaviness in left hypochondrium or splenectomy **(Hemolytic anemias**
- patient denied recent blood transfusion **(ABO incompatibility)**
- patient denied Hx of engorged neck veins , painful right hypochondrium , abdominal distension and lower limb swelling(**right heart failure)**
- patient denied Hx of valvular replacement **(prosthetic heart valve)**
- patient denied recent travel ,mosquito bite associated with rigor and chills (**malaria**)

B) Hepatic causes of jaundice

- no Hx of tape water use , eating from outside source , fever and pain in right hypochondrium **(Acute viral hepatitis A&E)**
- patient denied Hx of high risk sexual behaviour, IV drug abuse and unscreened blood transfusion**(HIV)**
- patient denied Hx of recent(occupational) exposure to sewerage**(leptospirosis)**
- patient denied IV drug abuse , tattooing and high risk sexual behaviour **(HBV &HCV)**
- patient denied Hx of high grade fever associated with rigor and chills and pain in right hypochondrium(**Liver abscess)**
- patient denied HX of chronic alcohol consumption (**Alcohol induced hepatitis)**
- patient denied Hx of sudden weight loss/gain , diabetes and obesity **(NAFLD)**
- patients denied Hx of joint pain , darkening of complexion and erectile dysfunction **(Hemochromatosis)**
- patients denied family Hx of liver disease , abnormal movements , fits and psychiatric illness **(Wilson disease)**
- patients denied family Hx of chronic whistling sound ,inhaler use associated with these symptoms(**alpha 1-antitrypsin deficiency)**
- patient denied Hx of joint pain , oral ulcer , skin rash , abnormal periods and white spots on skin (**autoimmune -hepatitis)**
- patient denied Hx of itching , easy fatigability and blood in stool associated with these symptoms **(PBC&PSC)**

Scanned with CamScanner

- patient denied Hx of weight loss, ↓ appetite, abdominal distension and right hypochondrium **(Hepatocellular carcinoma)**
- patient denied pregnancy-induced HTN and recent childbirth **(HELLP syndrome)**
- patient denied sudden abdominal distension ,abdominal pain and family HX of blood thinning medication **(Bud-chiari syndrome)**
- patient denied recent exposure to dry-cleaner , factory chemicals ,pipes and mushroom **(toxin induced hepatitis)**
- patient denied recent use of anti-TB , OCP , amiodarone , anti-epileptic medication and chronic use of steroid **(drug induced hepatitis)**

C (post-hepatic)

- patient denied HX of pain in right hypochondrium that is worse during fatty meals **(Gall stones)**
- patient denied HX of weight loss , ↓ appetite and heaviness in right hypochondrium associated with these symptoms **Carcinoma of hepatobilliary channels (CA of ampulla, pancreatic ,bile duct and liver metastases and lymphoma)**
- there is no HX of warms infestation or warms in vomiting **(parasitic infection)**
- there is no HX of recent upper GI procedures**(traumatic biliary strictures like post ERCP**
- there is no HX of chronic epigastric pain that radiate to back **(chronic pancreatitis)**

DDs of patient known case of CLD now presented with acute jaundice are

- Acute on Chronic Liver Disease
- Acute Decompensated Liver Disease

Scanned with CamScanner

APPROACH TO ABDOMINAL DISTENSION (Due to CLD)

P/C

Worsening of abdominal distension 8 days

My patient who is known case of HCV$^+$ and has HX OF abdominal distension for the last 2 years presented with worsening of abdominal distension for the last 8 days .it was gradual in onset and progressively worsening in time .swelling initially started in abdomen and followed by swelling of groin and finally involved the feet .it is aggravated by ↑ intake of water and salt and relived with medication that ↑ urination. Abdominal swelling is **associated** with……. .However, patient denied

DDs of Abdominal swelling (as part of generalized body swelling)

1) **CCF**

   Patient denied past Hx of IHD, valvular heart disease and engorged neck veins and pink frothy sputum associated with these symptoms

2) **Cor-Pulmonale**

   Patient denied Hx of previous lung pathology, like past HX of TB, HX of whistling sounds in breath, chronic use of inhalers and chronic productive cough

3) **CKD**

   Patient denied ↓ urine output, blood in urine, frothy urine, periorbital puffiness and Hx of fistula formation and dialysis

4) **Chronic Diarrhea(malabsorption)**

   Patient denied chronic loose stools

5) **Cancer of GI**

   Patient denied Hx of ↓ appetite, weight loss and lumps & bumps in the body

   - **CA esophagus** →Hx of difficulty in swallowing
   - **Stomach** → early satiety
   - **HCC** → heaviness in right hypochondrium and worsening og jaundice
   - **colorectal CA** →blood in stool and altered bowel habits
   - **ovarian CA** →heaviness in the B/L groin and weight loss
   - **lymphoma** →Hx of night sweats , paleness of complexion ,bones pain and lumps and bumps in the body

6) **CLD** (long case here , see care of CLD)

The above-mentioned 6Cs are differentials of generalized body swelling as well as abdominal swelling

DDs of only abdominal distension/swelling

1) abdominal TB→ HX of TB contact , weight loss , and loose motion
2) ovarian CA→ HX of heaviness in groin ,associated with ↓ appetite and weight loss
3) SLE→ HX of photosensitivity , oral ulcer , and hair fall
4) Cushing syndrome→ Hx of moon like face , bruising of skin and HX of newly diagnosed DM and HTN
5) hypothyroidism→ HX of cold intolerance , constipation and puffiness of face

Scanned with CamScanner

6) Budd-chiari syndrome/portal vein thrombosis →Hx of blood thinning medication, HX of OCP use and family HX of coagulation disorder.

CARE of Chronic Liver Disease

- Hx of blood transfusion ,tattooing/piercing and surgery (HCV)
- HX of iV drug abuse and high risk sexual behaviors**(HIV &HBV)**
- kindly see the causes of jaundice(pre& post hepatic and hepatic causes) most of them are **either risk factors or etiology of Chronic liver disease**

COMPLICATION of CLD

- **Hepatic encephalopathy**
  Hx of abnormal sleep pattern, altered sensorium and irritability
- **Hepato-renal syndrome (HRS)**
  No HX of ↓urine output,
- **Hepato-pulmonary syndrome (HPS)**
  No Hx of SOB on standing
- **spontaneous bacterial peritonitis (HSP)**
  No HX of high grade fever and abdominal pain
- **Hepatocellular carcinoma**
  There is no HX of ↓ appetite, RHC heaviness and worsening of jaundice
- **upper GI bleed**
- there is no HX of blood in vomiting and black tarry stool or HX of haemorrhoids
- **Coagulopathy**
  There is no HX of easy brusibility, purpura, and epistaxis

ITP (ask about investigations, treatment and procedures like endoscopy etc.)

Ask Relevant

PAM-HUGS-FOSS-TV -F

Examination Scheme

Integral part of CLD examination

- DRE
- genital examination (testicular atrophy , loss of male hair pattern)
- orthostatic hypotension (may signify upper Gi bleed)

Rest of the examination scheme is same as discussed in the blood in the vomitus section

Scanned with CamScanner

VIVA OF CLD

What are the stages of CLD?

1) Compensated stage
2) Compensated with varices
3) Decompensated stage
   - ruptured varices
   - ascites
   - encephalopathy
   - jaundice

How will you investigate this patient?

- **CBC** →↓HB & platelets and ↑MCV
- **coagulation profile** →prolong PT
- **LFTs**→↓Albumin , GGT
- **RFTs**→HRS
- **Ultrasonography**→ cirrhotic liver and nodules , ascites and splenomegaly
- **ECG**→prolong QT interval due to cirrhotic cardiomyopathy
- **ascetic tap** →SBP
- **endoscopy**→ varices
- **triphasic CT /MRI**
- **liver Biopsy /fibro-scan**
- **non-invasive investigations** as mentioned in upper GI bleed section
- **markers of fibrosis** →Hyaluronic acid ,type 3 collagen and Matrix Metalloproteinase inhibitors (MMP-inhibitor-1)
  - normal size of liver →16cm
  - normal size of spleen →12cm
  - portal vein size →0.6-1.2cm
  - CBD normal size →6-7mm

HOW WILL YOU TREAT /MANAGE CLD PATIENT?

For the CLD management follow below mention objectives

- Treatment of the underlying cause to slow down the progression of the disease
- Avoidance of superadded insult
- Medication adjustment
- Symptomatic treatment (ascetic tap)
- Prevention , identification and treatment of complications of CLD
- Assessment of patient for liver transplantation

General treatment measures for CLD patients

- avoid alcohol
- fluid and salt restriction
- use multivitamin

Scanned with CamScanner

- N-carnitine 300mg QID for muscle cramps
- vaccination of hepatitis A&B ,influenza and pneumococcal vaccination
- treat the cause
- diet chart → carb > fats > protein
- Do not share brush , comb , nail cutter

TREATMENT OF COMPLICATIONS

1) Upper GI bleed

See approach to blood in vomitus

2) ASCITES

- ascetic tap and measure SAAG ratio if the ratio is >1.1 it is due to portal HTN **(CLD)** and if the ratio is < 1.1 then ascites is due to non-portal hypertension
- **bed rest** →↑ renal flow
- **salt restriction** →up to one spoon (2gram)/day
- **water restriction** →1L per day if there is hyponatremia
- **severe hyponatremia(serum NA< 125mmo/L)** IV conviaptan 20mg (oral tolvaptan is contraindicated in liver disease)
- **protein intake** 0.5-0.7g/kg day
- **Diuretics** like spironolactone 100mg-400mg(max) or amiloride 5-10mg and furosemide 40-160(max)/day with target weight loss of 0.5-0.7kg/day
- if there is ascites is refractory to diuretics(**diuretic-resistant ascites**) or side effects develop than →
- **Paracentesis** (SE infection, bowel perforation and bleeding) 4-6L/Day under cover **of IV albumin** (6-8g/L of ascites).if **ascites still resistant** than TIPS
- **transjugular intrahepatic portosystemic shunt (TIPS)**
- via jugular route a stent is placed between hepatic and portal vein
- only as a bridging therapy until liver transplant .its adverse effects are hepatic encephalopathy , stent stenosis and septicemia
  - resistant ascites →does not respond to max diuretic therapy
  - intractable ascites →intolerable side effect of diuretic so dose can't be↑

3) Spontaneous bacterial peritonitis (SBP)

Diagnostic criteria

- Ascetic fluid WBC count > 500 cells/mcL
- neutrophil (PMN) > 250
- protein > 1g
- positive culture to one organism(80-90%) like E.coli or streptococcus spp

- SBP is characterized by fever , abdominal pain and worsening jaundice

➢ **Treatment of SBP**

- inj cefotaxime →fortum→2g BD or TDS for 5 days
- alternatives are ceftriaxone, Augmentin, and fluoroquinolones **(if patients not receiving** fluoroquinolones prophylaxis)

Scanned with CamScanner

- IV albumin 1.5 g/kg on day 1st and 1g/kg on day 3rd esp. if there is creatinine > 1mg/Dl ,total bilirubin > 4mg/dL and BUN > mg/dL
- Definite treatment is liver transplant
- effectiveness of treatment is monitored by ascetic tap after 48 hours where PMN count should be ↓ by at least 50% after initial therapy
- **features of secondary bacterial peritonitis**
  - **A)** bowel sound absent
  - **B)** growth of multiple organism on ascetic fluid culture
  - **C)** evidence of perforation
  - **D)** Guarding and rebound tenderness
  - **E) Runyon,s criteria for secondary bacterial peritonitis , 2 out of the 3 points**
    - glucose level of ascetic fluid < 50mg/dL
    - protein concentration > 10g/L
    - lactic dehydrogenase (LDH) > normal serum levels

Secondary Prophylaxis of SBP (lifelong)

- in patient with previous episode of SBP , the risk of the recurrent peritonitis may be decreased by long-term use of ciprofloxacin(500mg OD) ,norfloxacin (400mg OD) and Trimethoprim – sulfamethoxazole (OD double strength)
- in high-risk cirrhotic patients without prior peritonitis (these includes ,ascetic protein < 1.5g/dL , serum bilirubin > 3mg/dL , creatinine > 1.2mg/dL and Child-Pugh score of ≥9) , the risk of peritonitis(and heptorenal syndrome) and mortality for at least 1 year may be reduced by prophylactic Trimethoprim –sulfamethoxazole (OD double strength) term use of ciprofloxacin(500mg OD) and norfloxacin (400mg OD)

Non-antibiotic prophylaxis

- statin , bile acid and probiotic are under study

Prognosis of SBP→

Only 10-20% of patients survive for 5 years from the first appearance of ascites due to cirrhosis

- The overall mortality is high -30% during hospitalization and up to 70% by 1 year.

4) Heptorenal syndrome (HRS)

5) type 1 →rapidly decline in renal function in less than 2 weeks
Type 2→ chronic and slowly progressive decline in renal function

It is diagnosis of exclusion

Diagnostic criteria of HRS

1) advanced liver disease
2) ↑ serum creatinine 0.3mg /dL within 48 hours or increased by ≥ 50% or more from baseline within the previous 7 days
3) ↓urine output < 0.5ml/kg/hr for ≥6 hrs

Scanned with CamScanner

4) no improvement in renal function after at least 48-hours diuretic withdrawal and volume expansion with albumin

Treatment of HRS

- withhold diuretics
- IV albumin in combination with one of the following vasoconstrictors for 7-14 days (IV Terlipressin, noradrenaline and oral midodrine plus Octreotide subcutaneously or IV)
- **MARS therapy** →Molecular Adsorbent Recirculating System
- also called liver and renal dialysis that selectively remove –albumin bound substances

5) Coagulopathy

Treatment

- oral or IV vit-K for 3 days
- FFPs for active bleeding (alternate option is recombinant activated factor VIIa but it is expensive)
- if platelets is less than 50K than transfuse the platelets and if patients undergoes invasive procedure than additionally the thrombopoietin analog (avatrombopag , lusutrombopag) at least 3-5 days
- keep platelets > 50K to avoid coagulopathy

6) Hepatopulmonary Syndrome (HPS)

- it is triad of chronic liver disease , ↑alveolar-arterial gradient(on ABG paO_2 < 80mmhg)) and right to let shunt due to intrapulmonary vasodilatation
- it is characterized by SOB (platypnea) and desaturation (orthodeoxia) in the upright position
- **contrasted-enhanced echocardiography** is a sensitive screening test(detect pulmonary vascular dilatation) while **macroaggregated albumin lung perfusion scanning** is specific and confirm the diagnosis
- **HRCT** may be useful for detecting pulmonary vascular dilation that may be amenable to embolization

Treatment of HPS

- LTOT therapy
- TIPS as a bridging therapy
- Definite therapy →liver transplantation

7) portopulmonary Hypertension

- it is treated by agent like prostaglandin analog(epoprostenol, ilopprost or treprostinil), endothelin receptor antagonists(ambrisentan , macitentan while bosentan is hepatotoxic) phosphodiesterase-5 inhibitor (sildenafil ,tadalafil)) →**(Recent Advances/new agents)**oral prostacyclin receptor antagonists (**selexipag**) or cyclic GMP analog (**riociguat**) .they all reduce pulmonary hypertension
- beta-blocker are contraindicated as they worsen exercise capacity

And CCB may be used with caution because they worsen portal hypertension

Scanned with CamScanner

- liver transplantation is contraindicated in patients with moderate –severe hypertension (mean pulmonary pressure > 35 mm Hg)

8) Hepatic encephalopathy

Grades of hepatic encephalopathy

West-Heaven criteria

Clinical grades	Clinical Signs
Grade 1	poor concentration, slurred speech, slow mentation, disordered sleep rhythm
Grade 2	drowsy but easily rousbale, occasional aggressive Behaviour, lethargic
Grade 3	marked delirium, drowsy, sleepy but response to pain and voice, gross disorientation
Grade 4	unresponsive to voice, may or may not respond to painful stimuli.

What are the factors that precipitate hepatic encephalopathy?

- ↑protein load (GI bleed)
- constipation
- infection
- hypokalaemia
- dehydration
- portosystemic shunting
- Drugs (especially sedative and anti-depressant)

What are the DDs of hepatic encephalopathy?

- Drugs and alcohol intoxications
- Delirium tremens /alcohol withdrawal
- Wernicke's encepalotahy
- Hypoglycaemia
- intracranial bleed(sub and extradural)
- Post-ictal state
- primary psychiatric disorder

See pathophysiology of hepatic encephalopathy from a reference book

Treatment of hepatic encephalopathy

- **reverse (treat) the cause**
- avoid protein (intake should be 60-80g/day)
- Lactulose → causes of acidification of colon content and favour the formation of ammonium ion from ammonia that is not absorbable. Furthermore, it changes the gut flora so that fewer ammonia –forming organism are present. **dose is 30ml /QID** for 2-3 days .then dose should be titrated so the patient produces 2-3 soft stools /day
- retention enema →200/300mg/mL solution of lactulose in saline or sorbitol given rectaly while the patient is in left lateral position

Scanned with CamScanner

- oral (via NG) antibiotic rifaximin 550mg (↓NH_3) BD and/ or metronidazole 250mg 3 times daily may also be helpful
- oxazepam10-30 mg (or haloperidol) for marked agitation

Liver Transplantation

- Definite treatment of all complications of cirrhosis is, liver transplantation
- Mercedes-Benz incision for liver transplant

Indication for liver transplantation

1) acute liver failure (see king's collage criteria)
2) irreversible chronic liver disease (see MELD –score below)
3) early stage of HCC (see Barcelona criteria→see Rx of HCC)

5-year survival is ≥80% (post-transplant)

Transplant canters in Pakistan are **PKLI Lahore, shifa international hospital** Islamabad and **Gambat Sindh.**

Cost of transplant …

Model for End –stage Liver Disease (MELD/MELD-Na)

- It is based on the value of serum bilirubin, INR, serum creatinine and 6.4 (constant for liver etiology) and more recently serum sodium levels is also included .
- MELD score range from 6-40
- if score is ≥17 , is an indication for liver transplantation
- score ≥ 22 ,has high mortality
- apart from tool for liver transplantation, it is also a measure of mortality risk in patients with end –stage liver disease and is particularly helpful for predicting short and intermediate –term survival and complications of cirrhosis like SBP

Child-Pugh Class

- it is use to assess the prognosis (**severity and mortality**) of chronic liver disease , mainly cirrhosis
- it is based on values of ascites, Albumin, bilirubin , encephalopathy and prothrombin time
- remember it as **ABCDE** **A**→Albumin) **B**→bilirubin) **C** →coagulopathy →**PT** **D**→abdominaldistension →**ascites**) **E** → encepalotahy

Score	class	one-year survival
5-6	A	100%
7-9	B	80%
>9(10-15)	C	45%

SPECIFIC TREATMENT OF CLD

1). Non -Alcoholic Fatty liver Disease(NAFLD)

- ↑ALT , hepatomegaly and steatosis on ultrasonography
- liver biopsy→ it is diagnostic and shows macro vesicular steatosis with or without inflammation and fibrosis on liver biopsy

Scanned with CamScanner

- ANA , smooth muscles antibodies may be detectable in 30% of NASH patients
- NAFLD →takes almost **10 years** to progress **to CLD**
- principal causes of NAFLD are obesity , diabetes, hypertriglyceridemia in association with insulin resistance as part of metabolic syndrome
- Alternative name of NAFLD is **MAFLD** metabolic associated (or metabolic dysfunction associated) fatty liver disease

Treatment

- lifestyle modification like control weight loss(10%) , dietary fat restriction and moderate exercise
- avoidance of alcohol(although modest wine consumption may not be detrimental in non-smoker)
- Vitamin E 800 IU/day for non- diabetic
- thiazolidinedione(**causes weight gain**) and metformin for diabetic and non-diabetic patients
- pentoxifylline
- Ursodeoxycholicacid 12-15mg/kg/day
- obeticholic acid (farnesoid X receptor agonist) is approved treatment for PBC but also indicated in patients with NASH
- if lipid profile is deranged than statin is indicated
- Bariatric surgery →for patients having BMI > 35
- liver transplantation
- Takes 10 years to progress to CLD--------

Ultrasound Grades of NAFLD

0) **no steatosis (less than 5% hepatocytes contain fats)**
Normal echogenicity of liver parenchyma; Normal visualization of diaphragm and intrahepatic blood vessel

1) **Mild steatosis(6-33% hepatocytes contain fats)**
Slightly ↑ Echogenicity of liver parenchyma
Normal visualization of diaphragm and intrahepatic blood vessel

2) **Moderate Steatosis (34-66%)hepatocytes contain fats**
Markedly ↑↑ Echogenicity of liver parenchyma
Slightly impair visualization of diaphragm and intrahepatic blood vessel

3) **sever Steatosis (> 66% hepatocytes contain fats**
Severely ↑ Echogenicity of liver parenchyma
Diaphragm and intrahepatic blood vessel not visible

2) **Alcoholic liver disease**

- a recent period of heavy drinking , complaints of anorexia and nausea , and the demonstration of hepatomegaly and jaundice strongly favour the diagnosis of alcoholic –liver disease
- AST is > than ALT ≥ 2

Scanned with CamScanner

- ↑ transferrin saturation , hepatic iron stores and sideroblastic anemia are found in many alcoholic patient
- Liver biopsy may show micronodular cirrhosis, Mallory bodies and perivenular and perisinuosidal fibrosis.

Treatment

A) General measures

- abstinence from alcohol
- nutritional support (30-40)kcal/kg with 1.0-1.5g/kg as protein and sufficient amount of carbohydrate and calories to reduce endogenous protein catabolism , promote gluconeogenesis and prevent hypoglycaemia
- administration of micronutrient particularly folic acid , thiamine and zinc as glucose administration ↑ the thiamine requirement and can precipitate Wernicke –Korsakoff syndrome if thiamine is not co administered
- nephrotoxic drug should be avoided in patient with severe alcohol-associated hepatitis
- Acamprosate, naltrexone or baclofen are indicated for maintenance of alcohol abstinence in combination with counselling who are abstinent at treatment initiation.

B) **pharmacological treatment**

- Methylprednisolone, 32 mg/day orally or the equivalent ,for 1 month , may reduce short-term (1 month) mortality ,in patient with alcoholic-hepatitis and encephalopathy or a **Maddrey discriminant function index** (patient PT –control PT 4.6 + total bilirubin) **of ≥32 or a MELD score of ≥ 20**
  DF (4.6× increases in PT (sec) +Bilirubin (mg/dL)
- the combination of corticosteroid and N-acetylecystine may improve short-term survival , reduce the risk of heptorenal syndrome and infection
- pentoxifylline, 400mg TDS orally for 4 weeks reduces the risk of heptorenal syndrome .it is use when corticosteroids are contraindicated , however , it does not improve survival
- definite treatment is liver transplantation

Poor prognostic factors (short-term mortality)

- older age , serum bilirubin > 10mg/dL , hepatic encephalopathy , coagulopathy , azotemia , leukocytosis , sepsis lack of response to corticosteroids, low serum transferrin level and reversal of portal blood flow by Doppler .

Prognostic model of alcoholic –liver disease (Lille model)

That include (age, creatinine, serum albumin, PT/or INR and serum bilirubin on admission and serum bilirubin on 7th day of admission)

The combination of MELD score and Lille model is the best predictor of short-term mortality among the scoring system.

- While the most important **long-term** prognostic factor is continued excessive drinking. there is no safe level of drinking in persons with alcoholic –associated liver disease or other liver disease

Scanned with CamScanner

- in the UK , **a unit of alcohol contain 8 g of ethanol** and the latest public health has adopted a more conservative threshold of 14units /week for both men and women (while previous advice was 14units/ week for women and 21units /week)

3) Hemochromatosis

- inherited as autosomal recessive trait
- there are **4 subtypes of primary** hemochromatosis including juvenile-onset variant
- in hereditary hemochromatosis, iron is deposited throughout the body and total body iron may reach 20-60g (normally 4g)
- there is 15-20% ↑risk of HCC

Causes of Hemochromatosis

Primary Haemochromatosis
Hereditary haemochromatosis
Congenital acaeruloplasminaemia
Congenital atransferrinaemia
Secondary Iron overload
Parental iron loading (e.g. repeated blood transfusion)
Iron-loading anemia (thalassemia, sideroblastic anemia, pyruvate
Liver disease
Complex Iron Overload
Juvenile haemochromatosis
Neonatal haemochromatosis
Alcoholic liver disease
Porphyria cutanea tarda
African irons overload (Bantu siderosis)

Investigations

1) LFTs
2) Transferrin saturation > 45%
3) markedly ↑Ferritin , saturated plasma iron-binding capacity
4) HFE gene(mutation in HFE gene on chromosome 6)
5) C282Y and H63D
6) Biopsy
7) CT/MRI →may show changes consistent with iron overload
8) hepatic iron index (umol of iron per g dry weight of liver/age in years) > 1.9 suggest primary hemochromatosis

- for general population iron studies while those who have positive family history HFE gene should be ordered

Rx of haemochromatosis

- avoid foods rich in iron (such as red meat) , alcohol , vitamin C , raw shellfish and supplemental iron

Scanned with CamScanner

- Phlebotomy ---- weekly venesection of 500 ml (250 mg iron) weekly until the serum iron is normal (may takes 2-3 years)
- once ,iron store depletion is achieved(iron saturation less than 50% and serum ferritin level 50-100mcg/L) , phlebotomies should be done 2-4 monthly to maintain serum ferritin levels between 50-100mcg/L
- **PPI may ↓** frequency of phlebotomy
- chelating agent deferoxamine(20-40mg/kg/day infused over 24 hours) is indicated for patient with hemochromatosis and anemia or those with secondary iron overload due to thalassemia who cannot tolerate phlebotomies(available two oral chelator are , deferasirox(20mg/kg OD and deferiprone 25mg/kg TDS/day) .
- treatment of complications
- liver transplantation

Complications:

Reversible

- Heart failure (dilated cardiomyopathy)
- Skin pigmentation
- Hepatomegaly

Non-reversible

- Joint disorders
- Hypogonadism
- Diabetes mellitus

4) Wilson' disease

- autosomal recessive disorder of copper metabolism caused by a variety of mutations in the ATP7B gene
- in Wilson's disease , there is almost always a failure of synthesis of caeruloplasmin; however, some 5% of patient have normal circulating caeruloplasmin
- it has wide range of presentation including **liver disease ,neuropsychiatric** and **coombs negative hemolytic**

Investigations

Leipzig criteria

- Demonstration of ↑urinary copper excretion (> 40mcg/24 hours and →Low serum ceruloplasmin levels (less than 14mg /dl (140mg/L) and less than 10mg/dl (100mg/L) strongly suggest the diagnosis and elevated hepatic copper concentration (greater than 250mcg /g of dry liver) as well as KF rings and typical symptoms.
- measuring 24-hour urinary copper excretion while giving D-penicillamine is a useful confirmatory test (more than 25 umol/24 hrs is considered diagnostic of Wilson's disease in children →**CMDT say it lack sensitivity)**
- MRI brain →evidence of ↑ copper in basal ganglia , brainstem and cerebellum

Scanned with CamScanner

- Slit lamp examination for Kf- rings (also positive in other causes of obstructive jaundice?)

Rx

- treatment before patient became symptomatic
- ↓ intake of diet rich in copper like shellfish , organs food,nuts, mushrooms and chocolate → dry food Band hai
- oral D-penicillamine (Vistamin 750-2000 mg/day, MOA→ ↑ urinary excretion of copper) take 1 hour before or 2 hours after food along with oral pyridoxine 50mg / week
- adverse effects of D-penicillamine includes GI disturbance ,autoimmune reactions , nephrotoxicity and bone marrow depression
- trientine(250-500mg TDS MOA→ ↑ **urinary excretion of copper**) is when D-penicillamine is no tolerated or serious adverse effects develop
- Zinc acetate or zinc gluconate (50 mg TDS 1 hour before or 2 hours after foods MOA→ ↓ GI absorption of copper and ↑ faecal excretion) is 1st line therapy in asymptomatic, pregnant patients and those with neurologic disease. if should be used in combination with other chelating agent or as maintenance therapy (after decoppering with a chelating agent)
- Bis-choline tetrathiomolybdate(**Recent advances**) ↓ GI copper absorption and showed promising result as an initial therapy for neurologic diseases
- liver transplantation is indicated for fulminant liver failure(may be precipitated by sudden withdrawal of chelating agent) or for advanced cirrhosis with liver failure
- siblings and children's of patients with Wilson's disease must be investigated and treatment should be given to all affected individuals, even if they are asymptomatic

The treatment should be continuing lifelong. Once the serum copper level is within normal range (50-150mcg/L) the dose of chelating should be ↓ to the minimum maintenance and during pregnancy the dose of penicillamine and trientine should be↓ but do not stop the treatment.

Prognosis → prognosis is excellent, provided treatment is started before there is irreversible damage

5) Autoimmune Hepatitis

There are three types of autoimmune hepatitis

Type i)

- it is also called classic autoimmune hepatitis
- ANA and anti-smooth muscle antibody are positive
- the Eliza(EIA) for antibody to HCV may be falsely positive in type 1 autoimmune hepatitis
- antibodies to soluble liver antigen(anti-SLA) characterize a variant of type I that is marked by severe disease, a high relapse rate treatment and absence of the usual antibodies(ANA and smooth muscle antibodies)

Type ii)

- it is more common in young girls
- it is characterized by positive antibodies to liver-kidney microsome type 1 (anti-LKM1) particularly in children and adolescent

Scanned with CamScanner

- ANA & anti-smooth muscle antibody are negative
- in some cases , antibodies to liver cytosol type 1 may be positive
- it may be associated with PBC(7-13%) &PSC 6-11%) called **overlap-syndrome** and diagnosis is based **on Paris criteria**

Type iii)

- it is characterized by positive anti-soluble liver antigen and anti-liver pancreas antibody
- it carries worst prognosis

Apart from specific antibodies, ALT may be raised > 1000 units/L and bilirubin is also ↑ in all types of autoimmune hepatitis. Characteristic biopsy finding is interface hepatitis with, or without hepatitis

Types of autoimmune hepatis			
	Type 1	Type 2	Type 3
Epidemiology	Classic type Around 80% of AIH	Around 10% of AIH more prevalent in children	Small subgroup
Clinical feature	Chronic or acute palmar erythema and spider naevi common		Similar to type 1
Autoantibodies	Both ANA and SMA (directed at actin) Antibodies present in 40-50% SLA/LP antibodies in 20% _in half of these the only demonstrable antibody (ANA /SMA /LKM antibodies may be found in other disease ; SLA /LP antibodies highly specific for AIH but missed on routine immunofluorescence	LKM antibodies directed at cytochrome p450lld6	SLA antibodies directed at UGA suppressor and TRNA –associated protein
Other tests	Polyclonal (especially lgG) Hypergammaglobulinaemia	Type 2b associated with LKM antibodies and HCV infection	ANA/SMA/LKM antibodies not present No significant hypergammaglobulinaemia
Treatment	Corticosteroids	Corticosteroids (rapidly progressive without treatment)	Corticosteroids (rapidly progressive without treatment)

Scanned with CamScanner

Treatment of Autoimmune Hepatitis

- there are two approaches , one is oral (or IV) steroid and the dose is gradually reduce and once the LFTs(and the patient) is normal ,start the steroid sparing agent while the other approach is start with steroid and after 2 weeks, introduce the steroids sparing agent's
- ,In the first approach, prednisolone 60mg orally daily (or equivalent IV) is initiated and tapered weekly depending upon the response to treatment , to a maintenance dose of 10mg /day .this regimen is proffered in severe hepatitis
- in patient with non-cirrhotic autoimmune hepatitis , budesonide , 3mg TDS as first line therapy is as effective as prednisolone
- While in 2nd approach 30mg prednisolone (30mg orally daily) is started followed by azathioprine 50mg orally daily. Steroids is gradually tapered to 10 mg/day.
- A↓ in serum AST levels by 80% after 8 weeks predict normalization of AST at 1 year
- once complete remission is achieved, therapy may be withdrawn, but the subsequent relapse is very high (90% by 3 years)
- relapse may be treated in the same way as the initial episode with the same remission rate
- During pregnancy, flares can be treated with prednisolone and maintenance azathioprine does not have to be discontinued.
- Those not responding to corticosteroids and azathioprine (failure of serum aminotransferase level to decrease by 50% after 6 months) may be considered for trials of cyclosporine, tacrolimus, methotrexate, and rituximab and mycophenolate mofetil.
- Liver transplantation →indicated for treatment failures and patient with a severe acute presentation but the disease has been recognized to recur in up to 70% of transplanted livers at 5 years as immunosuppression is reduced
- The response rate to therapy with prednisolone and azathioprine is 80% with the remission in 65% by 3 years .poor prognostic factors includes young age, ↑MELD score and raised bilirubin.
- blood counts are monitored weekly for the first 2 months and then monthly thereafter because of the small risk of bone marrow suppression
- while symptomatic improvement of patient is often rapid , however , biochemical improvement (normalization of aminotransferase) is gradual and after an average of 22 months .furthermore , histological resolution of inflammation lags biochemical improvement by 3-6 months (takes an average of 2.5 years)

6) Primary Biliary Cirrhosis (PBC)

- it is also called primary biliary cholangitis
- it is chronic progressive cholestatic liver disease that predominantly affects women aged ≥ 30 years
- it is characterized by destruction of small intrahepatic bile ducts

Investigations

- ↑ALP (cholestatic picture

Scanned with CamScanner

- base line ultrasonography
- Anti –mitochondrial antibodies (AMA-95% sensitivity) when AMA is negative than diagnosis should not be made without histological evidence and cholangiography(MRCP) to exclude other biliary disease
- ANA and anti –smooth muscle antibodies are positive in 15% of patient
- **Histological staging OF PBC**(in case of AMA negative PBC)
  1) portal inflammation with granuloma
  2) Bile duct proliferation and periporatl inflammation
  3) interlobular fibrous septa
  4) cirrhosis

Management

A) For pruritus
- cholestyramine(4g) in water or juice TDS
- Rifampin 150-300 mg BD
- opioid antagonist(like naloxone 0.2mcg/kg/min IV infusion or oral naltrexone 12.4 mg /day)
- ondansetron 4mg TDS or sertraline 75-100mg /day

B) For refractory pruritus
- plasmapheresis or extracorporeal albumin dialysis e.g. MARS therapy

C) fatigue
- once hypothyroidism, depression and celiac diseases have been excluded , currently there is no specific treatment available for fatigue ,however for day time somnolence , modafinil 100-200mg/day is indicated which is poorly tolerated by most patients

D) fat soluble vitamins (ADK) supplements .it is strongly indicated in case of malabsorption (there is ↑ incidence of celiac disease in PBC) and bone disease

E) Ursodeoxycholicacid (13-15mg/kg/day) is the preferred 1st line medical therapy in PBC. It ↓ the progression of the disease, stabilize the histology and improve the long-term survival .it also ↓ the risk of recurrent colorectal adenomas in patients with PBC. this drugs is associated with weight gain and sometime loose stools

F) The 2nd line agents are bezafibaret and fenofibrate (activates peroxisome proliferator – activated receptors PARSs) and inhibit bile acid synthesis .it improve liver biochemistry and fibrosis.

G) colchicine and methotrexate has also been reported to improve symptoms and ALP& bilirubin level

H) **obeticholic acid(⊿ Recent advances)** it is farnesoid-X receptor agonist and approved by FDA in 2016 for the treatment of PBC and it has been shown to stabilize or revers the fibrosis .it is indicated for patient with incomplete response to ursodeoxycholicacid, dose is 5-10mg/day .it adverse effect is primarily pruritus .

I) liver transplantation
- once symptoms develops , without liver transplantation survival averages 7-10 years

Scanned with CamScanner

- indicated for liver transplantation are , MELD-Na ≥15 , total bilirubin at least 6 or Mayo-risk score at least 7.8
- post-transplant 1-year survival is 85-90%
- The PBC recur in graft in 20% by 3 years and 37% by 10 years.

7) **Primary Scleroing Cholangitis (PSC)**

- it is cholestatic liver disease that involve the entire biliary tree and leads to obliteration of intra-hepatic and extrahepatic bile ducts and ultimately biliary cirrhosis
- PSC is more twice common in young men aged 25-40 years and often associated with ulcerative colitis

nvestigations

- LFTs may show cholestatic picture ↑ALP &bilirubin and mildly raised transaminase
- in addition to ANCA, low titer of ANA and anti-smooth muscle antibody and anti-saccharomyces cerevisae may be positive but has no diagnostic significance , serum AMA is absent
- 1st line investigation is MRCP →reveal multiple irregular structuring and dilation
- Gold standard investigation is ERCP →diagnostic and therapeutic
- liver biopsy→ when MRCP &ERCP is normal with typical symptomatology , the disease may be confined to small intrahepatic bile duct in about 15% of cases and liver biopsy may be indicated that may show characteristics periductal fibrosis (onion-skinning) and in advanced stage biliary cirrhosis; obliterative cholangitis leads to the so-called vanishing bile duct syndrome

Management

- acute attack of bacterial cholangitis may be treated with ciprofloxacin 750mg BD
- ursodeoxycholicacid 10-15mg/kg may improve the liver chemistry but does not change the natural course of the disease
- if cholangiography shows obstruction of extra-hepatic bile ducts , mechanical relief can be obtained by placement of a stent or by balloon dilatation performed at ERCP
- Fat-soluble vitamins in malabsorption and bone disease
- for pruritus same treatment as for PBC
- cholecystectomy when gall bladder polyps is > 8mm
- in patients with ulcerative colitis ,PSC is an independent risk factor for the development of colorectal dysplasia and cancer and therefore surveillance colonoscopy yearly for patient with UC and 5 yearly without UC should be carried out
- liver transplantation is indicated in case of cirrhosis and decompensation but disease may recur in graft in 30% of the cases and post-transplant 1-year survival is 90% and 5-year is 70%
- without transplant →average survival is 21 years

Complications of PSC

Scanned with CamScanner

A) Cholangiocarcinoma

- Cholangiocarcinoma may complicate the PSC in 20% of the case
- A serum CA 19-9 level above 100 units/mL is suggestive but not diagnostic
- annual MRI with MRCP and ultrasonography are recommended for surveillance

B) Colorectal neoplasia

Patient with PSC and associated ulcerative colitis is at high risk (10 folds higher than PSC without UC) for colorectal neoplasia

C) there are ↑ risk of gall stones , cholecystitis , gallbladder polyps and gall balder carcinoma in patients with PSC

8) Budd-chiari syndrome

- characterized by thrombosis of the larger hepatic veins and sometimes the inferior vena cava
- primarily due to inherited or acquired hypercoagulable states
- etiology may be identified in 45-75% of the cases
- myleoproliferative disorder (polycythaemia Vera) is the most common risk factor among all

Investigations

- LFTS→ vary considerably depending upon the presentation and sometime can mimics acute hepatitis
- screening test of choice is contrast –enhanced , or color –Doppler ultrasonography(85% sensitivity) that may detect hepatic venous or inferior vena caval thrombosis
- Ct and MRI may also demonstrate same finding as mentioned above
- CT →may show a prominent caudate lobe of the liver
- venography is needed only if CT and MRI are unable to demonstrate the hepatic venous anatomy clearly
- ascetic fluid tap may show exudative picture in the early stages
- liver biopsy rarely done and may show centrilobular congestion and fibrosis
- investigate for the underlying causes /risk factors

Scanned with CamScanner

Treatment

- predisposing causes should be treated as far as possible
- Where recent thrombosis is suspected, infusion of a thrombolytic agent like streptokinase into occluded veins and followed by heparin or oral anticoagulants (warfarin) should be considered for life long. however, anticoagulation is associated with high risk of bleeding particularly in patient with portal hypertension and those undergoing invasive procedures
- short hepatic venous strictures and inferior vena caval web can be treated with balloon angioplasty
- if above measures fail or in case of more extensive hepatic vein occlusion, many patient can be managed successfully by insertion of a covered TIPSS followed by anticoagulation
- when TIPSS is technically not feasible because of complete obstruction of hepatic vein obstruction , then ultrasound guided direct intrahepatic portosystemic shunt is an alternative approach
- liver transplantation in case of acute liver failure , cirrhosis with decompensation and failure of a portosystemic shunt .the 1 and 10-year survival post-transplant is 85% and 69% respectively
- treatment of the complication like ascites that is initially treated medically but often with limited success
- treatment of the underlying cause like myleoproliferative disorder with hydroxyurea

Prognosis

- the overall 5-year survival rate is 50-90% with treatment but less than 10% without treatment
- Poor prognostic factors includes old-age , high child-Pugh score , ascites , encepalotahy , raised bilirubin , prolong PT , ↑ creatinine , acute on chronic liver disease and concomitant portal vein thrombosis

Sinusoidal Obstruction Syndrome (SOS)

- it is also called veno-occlusive disease
- It is rare condition characterized by widespread occlusion of the small central hepatic veins. It **clinical features are similar** to those of the Budd-Chiari syndrome but investigation show evidence of venous **outflow obstruction histologically** , but **in contrast to** Budd-Chiari syndrome , the larger **hepatic veins appear patent radiological**
- transjugular liver biopsy (with portal pressure measurement) may facilitate the diagnosis
- SOS may occours in-patient who have undergone hematopoietic stem cell transplant particularly those with pre-transplant ↑ aminotransferase level or fever with cytoreductive therapy with cyclophosphamide, azathioprine, busulphan and high dose total body irradiation. Additionally, some cytotoxic agents and pyrrolizide alkaloids (comfrey or bush tea) may also cause SOS.

- treatment is supportive but **recently** Defibrotide **(→Recent Advances)** that ↑ tissue plasminogen activator levels has been approved by FDA for prevention and treatment of

Scanned with CamScanner

sinusoidal-obstruction syndrome .It should be given as IV every 6 hours for at least 21 days .it adverse effect include hypotension and hemorrhage

(9) Alpha$_1$-Antitrypsin Deficiency

10) Hepatocellular Carcinoma (HCC)

- HCC is associated with cirrhosis in 85% of cases
- HBV (including occult infection) is a major risk factor

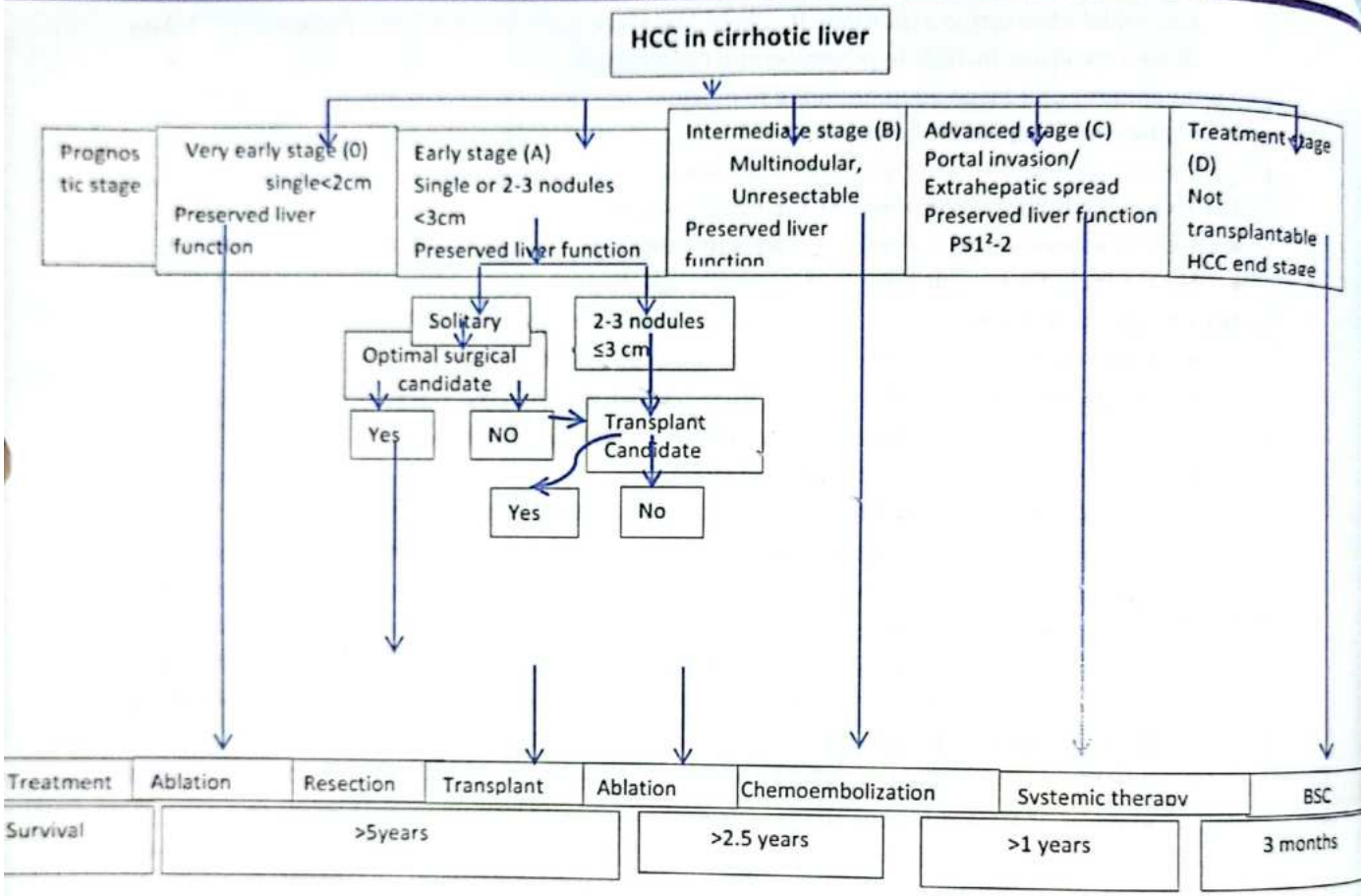
Investigations of HCC

- **CBC →** may show leukocytosis , as opposed to leukopenia
- **ultrasonography** →it ll detect liver lesions as small as 2-3cm and may also show evidence of portal vein involvement and features of cirrhosis
- **Viral serology** → like anti-JCV and HbsAg
- **Alpha-fetoprotein** → may be elevated in 70% of HCC patient
- **multiphasic helical CT and MRI with contrast enhancement** are the preferred imaging studies (MRI may be more sensitive than CT particularly in small lesion) to determine the location and vascularity →the typical hall mark is the combination of hypervascularity in late arterial phase (defined as arterial phase hyperenhancment [APHE] and washout on portal venous and or /delayed phase , which reflect the vascular derangement occurring during hepatocarcinogenesis
- **PIVKA-II (PROTEIN INDUCED BY VITAMIN K ABSENCE –II) .it is the latest marker of HCC (having diagnostic and prognostic importance)**
- **Liver biopsy** →histological confirmation is advisable in patients with large tumor who do not have cirrhosis or viral hepatitis , in order to confirm the diagnosis of HCC and exclude metastatic liver disease
- **screening & prevention** →screening for HCC , by ultrasonography and AFP measurement at 6-months intervals is indicated in high risk patient (includes individuals with cirrhosis caused by hepatitis B&C, alcohol , Haemochromatosis , NASH and alpha$_1$ antitrypsin deficiency) who would be suitable for therapy if diagnosed with HCC

Staging systems and treatment allocation of HCC

- **The treatment allocation recommended is according to Barcelona –Clinic LIVER CANCER (BCL C)** classification. Patients with HCC are classified into five stages (O, A, B, C AND D) according to pre-established prognostic variable, and therapies are allocated according to treatment-related status.
- prognosis prediction is defined by variable related to tumour status (size, number, vascular invasion , N1,M1), liver function (bilirubin, portal hypertension, liver function preservation)and performance status (ECOG).treatment allocation incorporates treatment dependent variables which have been shown to influence therapeutic outcome , such as bilirubin , portal hypertension or presence of symptoms

Scanned with CamScanner



Hepatic resection

This is the treatment of choice for non-cirrhosis patients .the 5 year survival in this group is about 50% .there is a 50% recurrence rate at 5 year however, which may be due to a second de novo tumour or recurrence of the original tumour. Few patients with cirrhosis are suitable for hepatic resection because of the high risk of hepatic failure nevertheless: surgery is offered particularly to some cirrhotic patients with small tumours and good liver function (child Pugh A with no portal hypertension)

Liver transplantation

Transplantation has the benefit of curing underlying cirrhosis and removing the risk of a second de novo tumour in an at risk patients .the requirement for immunosuppression creates its own risks of reactivation however if residual or metastatic disease is present and assessment of patients for suitability for liver transplantation focuses on the exclusion of extrahepatic disease and vascular invasion .the 5 year survival following liver transplantation is 75% for patients **with single tumours of less than 5 cm in size or three tumours smaller than 3 cm(the Milan criteria**).unfortunately the underlying liver disease in particular hepatitis c may recur in the transplanted

Scanned with CamScanner

liver and can result in recurrent cirrhosis that gives rise to a de novo HCC risk now complicated by the presence of immunosuppression

Percutaneous therapy

Percutaneous ethanol injection into the tumor under the guidance of ultrasound is effective treatment (80% cure rate) for tumors of ≤3cm. the recurrence rates (50% at 3 years) are similar to those of surgical resection . Radiofrequency ablation, using a single electrode inserted into the tumor under radiological ablation is an alternative that takes longer to perform but may cause more complete tumor necrosis

Trans –arterial chemo-embolization (TACE)

TACE with drug-eluting beads, transarterail chemo infusion (TACI), and transarterail radio embolization (TARE) via hepatic are not only palliative but may also prolong survival in patients with a large or multifocal tumor in the absence of extra hepatic spread .TACI and TARE are suitable for patient with portal vein thrombosis .TACE is contraindicated in decompensated cirrhosis and multifocal HCC

Chemotherapy

Sorafenib (an oral multikinase inhibitor of Raf Kinase, the VEGF receptor) prolong median survival and time to radiological progression in-patient with advanced HCC and until recently was the standard care in these patients .Lenvatinib is another agent with same MOA FDA approved for HCC.

- **Recent advances in HCC** combination of atezolizumab (an immune check –point inhibitor) and bevacizumab (an antibody to the VEGF receptor) is superior to sorafenib and is 1st line therapy for HCC
- the combination of Nivolumab (immune check point inhibitor) and ipilimumab has been recommended as second line therapy after failure of sorafenib
- **Regorfenib** an oral multikinase inhibitor that provides survival benefit for patients whose disease progresses despite sorafenib therapy

Prognosis depends on tumour size, the presence of vascular invasion and liver function in those with cirrhosis. Screening has improved the outlook through early detection

Factors that ↓ the incidence of HCC

- coffee, fish , polyunsaturated acid and metformin

What are the metabolic abnormalities, which may be found in hepatoma?

- polycythaemia
- hypoglycaemia
- Hypercalcemia
- porphyria cutanea tarda

Why secondary carcinoma is more common in the liver

It is due to high blood flow in liver and double blood supply by portal vein and hepatic artery

Scanned with CamScanner

PANCREATIC CA

P/c obstructive jaundice or
Mass in epigastric region

RECA

There is no HX of smoking, chronic alcohol intake, family HX of pancreatic CA or GI malignancy .patient also denied prolong epigastric pain with diarrhea or insulin depended DM

COMPLICATION

complication due to metastases from head to toe like altered sensorium, fits , chest pain cough , altered bowel habit , jaundice , itching , skin rash , bones pain B/L legs swelling and generalized body swelling etc.

INVESTIGATIONS

- CBC →anemia
- RBS or OGTT→ 10-20% patients has glucose intolerance or diabetic
- LFTS→ obstructive jaundice
- CA-10-9 (has sensitivity of 70% and specificity of 87%)
- multiphasic thin –cut CT abdomen →initial test of choice as it detect mass in more than 80% cases
- ultrasonography→ not reliable due to intestinal gas .however endoscopic ultrasound (EUS) is more sensitive than CT for detecting pancreatic cancer
- MRCP/ERCP → in case there is ambiguous CT or MRI finding

What are the 4 characteristics of pancreatic CA?

1) epigastric lump
2) thrombophlebitis(redness and swelling in IV Cannulation sites)
3) infective endocarditis
4) hypercoagulable state like DVT and /or portal vein thrombosis

What is Courvoisier sign or law? .

A palpable gallbladder in a jaundiced patient is usually the consequence of distal biliary obstruction by a pancreatic cancer.

What is the commonest type of carcinoma of pancreas?

Adenocarcinoma is the most common type (90%) and it arises from the epithelium of pancreatic duct

What are the common sits of pancreatic CA

- Head of the pancreas → 60%
- Body or tail of pancreas →20%
- combined (all three) → 20%

Scanned with CamScanner

Management

- Radical pancreaticoduodenal resection (whipple procedure) if cancer is strictly limited to the head of the pancreas , peri ampullary area and duodenum
- adjuvant chemotherapy with gemcitabine5 -fluorouracil, or gemcitabine with capecitabine is superior to no adjuvant therapy .Gemcitabine with capecitabine and a modified FOLFIRINOX (5 –fluorouracil, leucovorin, irino tecan, oxaliplatin) regimen have been found to be superior to gemcitabine along
- In metastatic cancer palliative care like endoscopic stenting of the bile duct, relive pain etc should be considered

Prognosis

Pancreatic CA particularly in head or tail has poor prognosis as most of the patients (80-85%) present with advanced or unresectable disease. 5 –years survival is 2-5%

Scanned with CamScanner

APPROACH TO PER RECTAL BLEED (As case of IBD)

P/C Blood in Stool 15 days

HOPI (ODPARAV)

DDs

1) **Hemorrhoids**
   There is no HX of chronic constipation, HX of skin tag in perianal area and Hx of excessive straining
2) **CA Colon**
   There is no HX of ↓ appetite, lumps & bumps in the body and sense of incomplete evacuation
3) **ischemic colitis**
   Patient denied Hx of DM, ↑ cholesterol and abdominal pain following meals ,associated with these symptoms
4) **IBD** long case ,see CARE
5) **Dysentery**
   There is no HX of high grade fever and warms in the stool
6) **Anal fissure**
   There is no HX of splashing of blood in the toilet seat during defecation and along with perianal pain
7) **CLD (as Hemorrhoids)**
   There is no HX of chronic HBV&HCV infection, blood in vomitus or black tarry stool
8) **CKD**
   There is no HX of pedal edema, ↓ urine output and sallow complexion of skin
9) **Colitis**
   There is no HX of prolong intake of antibiotics
10) **Aortic stenosis (as Hides Syndrome)**
    There is no HX of valvular lesion or HX of SOB or syncopal attack on exertion
11) **Radiation induced colitis**
    There is no HX of recent exposure to radiation
12) **Drug induced bleeding disorder**
    There is no HX of prolong intake of pain killer or blood thinning medication
13) **autoimmune /vasculitis**
    There is no HX of joint pain, skin rash, oral ulcer, palpable rash on buttocks & thigh and blood in sputum
14) **Haematological malignancy**
    There is no Hx of recurrent infection, night's sweats and heaviness in left hypochondrium
15) **Chronic infection like HIV , TB and celiac disease present with blood in stool**

Scanned with CamScanner

There is no HX of IV drug abuse, high risk sexual behaviour, gluten sensitivity and contact with TB patient

16) Diverticulitis

There is no HX of constipation and pain in left side of the abdomen associated with these symptoms

- PR bleed cases in exam are most likely IBD or CA Colon

CARE OF IBD

- patient denied HX of smoking
- there is no family HX of PR bleed (IBD & similar disorders)
- there is no HX of redness of eyes, pain or dryness in eyes , mouth ulceration ,SOB and dry or productive cough
- there is no HX of large joint pain ,skin brusibility , frothy urine , painful micturition or HX of stone in the urine
- patient denied silver skin lesions , pitting of nails , genital and oral ulcerations and Hx of low back pain with stiffness (**seronegative arthritis PAIR)**
- there is no HX of itching , fatigability and yellow discoloration of sclera **(PSC)**

COMPLICATIONS

Ask about complications like life threatening acute flare, surgery due to refractory nature of the disease, fistulas formation, obstructions, malabsorption (crohn's), anemia due to recurrent blood loss, GI malignancy and complications due to medications

ITP of IBD (investigations→ see below , treatment and procedures)

Ask relevant **PAM-HUGS-FOSS-TV –F**

Examination

Vitals (orthostatic hypotension → may signify active GI bleeding)

GPE→ clubbing ,dehydration, signs of malnutrition , pigmentation , lymph nodes , scratch marks anemia , jaundice , uveitis as red eyes oral ulcers , erythema nodosum and pyoderma gangrenosum

DRE and genitourinary examination → compulsory part of abdominal examination in IBD where you may finding blood or mass

Tenderness and abdominal distension may signify toxic megacolon, look for fistula formation, scar marks

MSK → sacroiliac joints, spine and peripheral joints examination

Rest of the systemic examination should be done quickly and mostly not contributory

Based on HX and clinical examination my differential diagnoses are (depending on your case)

1) IBD
2) infective colitis (due to bacterial , viral or protozoal
3) Microscopic colitis
4) CA colon (or ischemic colitis in middle age with predisposing factors)

Scanned with CamScanner

VIVA OF IBD

How will you investigate this patient?

- CBC→ anemia due to↓ iron , folic and B 12 and ↑TLC &platelets
- ESR and CRP→ may be ↑in exacerbation
- Albumin →↓ due to protein losing enteropathy
- LFTS → for obstructive jaundice
- Faecal calprotectin→ highly sensitive for detecting GI inflammation even when CRP is normal and useful for monitoring disease activity
- stool microscopy ,culture and R/E for detecting clostridium difficile, ova and cysts even in established cases of IBD to exclude superimposed enteric infection
- x-ray abdomen in case of flare →dilatation of colon and mucosal edema as demonstrated by thumb-printing sign

Specific investigations

- ileocolonoscopy→ in order to evaluate disease extent and to differentiate, if possible , between crohn's and UC and biopsy taken to exclude dysplasia
- Flexible sigmoidoscopy→ during acute flare as ileocolonoscopy may confer unacceptable risk
- enteroscopy& capsule endoscopy particularly in crohn's is useful in the identification of small bowel inflammation (avoid the latter in the presence of strictures)
- upper GI endoscopy and biopsy in patient with crohn's
- CT colonogram is alternative investigation if colonoscopy is incomplete or not tolerated
- Barium enema →it is less sensitive than colonoscopy and barium-follow –through demonstrate affected area of intestine as as narrow and ulcerated and often with multiple strictures .however , it is largely gas been replaced now by MRI enterography(that does not involve exposure to radiation)

How will you manage this patient?

1) ulcerative colitis (UC)

- it is an idiopathic inflammatory condition that involve the mucosal surface of the colon resulting in diffuse friability and erosions with bleeding
- smoking and appendectomy is protective e.g. ↓ the risk of UC
- approximately , 1/4th of patient have disease limited to the rectosigmioid region (proctosigmoiditis) , 1/4th have disease that extend up to splenic flexure (left-sided colitis) and 1/4th of the patients have disease that extends more proximally (extensive colitis)

Treatment

A) Mild to moderate proctosigmoiditis

- topical mesalamine& corticosteroid or oral aminosalicylate(5-ASA) .where topical mesalamine is superior than topical corticosteroid and oral 5-ASA and it is administered as a suppository 1000mg once daily for proctitis and as enema 4g daily for proctosigmoiditis for 4-8 weeks
- steroids in the form of hydrocortisone 80-100mg (enema or foam) or budesonide foam

Scanned with CamScanner

- if both are ineffective, than oral 5-ASA should be considered
- for patient with distal disease , who do not improve and topical& oral mesalamine , then following options may be considered 1) combination of oral and topical agent with an oral 5-ASA AGENT(2) topical corticosteroid (3) addition of oral prednisolone or budesonide for 4-8 weeks
- most patients with proctitis or proctosigmoiditis who achieve complete remission with oral or rectal 5-ASA should be continue indefinitely while topical steroid are ineffective for maintaining remission of distal colitis

B) Colitis

(Mild to moderate)

- UC above the sigmoid colon is effectively treated with both orally and rectaly 5-ASA
- for induction of remission , combination of oral 5-ASA (2-3g OD) and mesalamine suppository 1g or 4g enema at bedtime for 4-8 weeks .sulfasalazine is used as alternative or add-on therapy with folic acid
- if patient is still symptomatic after 4-8 weeks with above therapy , oral corticosteroid (like prednisolone or budesonide) for 4-8 weeks
- patient who require more than once course of steroids therapy every 1 -2 years for symptomatic relapses , treatment should be step-up to include a thioupurine like azathioprine or biological agent

(Moderate to severe colitis)

- Oral steroids like prednisolone 40mg/day is prescribed as 1st line agent (or 2nd line therapy in patient in whom initial 5-ASA was in effective) .improvement is observed in majority of patients within 2 weeks and after improvement prednisolone dose should be tapered by 5-10mg/week. after remission , mesalamine (2-4g/day) should be continued indefinitely while azathioprine may be helpful in steroid withdrawal
- tofacitinib(anti-Janus –kinase) or biological agents are indicated when steroid cannot be withdrawn completely (due to recurrent flares) or who require more than one course of corticosteroids every 1-2 years
- **2nd line therapy** if above therapy is not successful than anti-TNF antibodies (infliximab and golimumab) , integrin antibody (vedolizumab) ustekinumab(IL-12/23 antibody) and tofacitinib are the preferred treatment options for moderate to severe colitis depending on patient choice and prior exposure , response to biological agent , disease severity and comorbidities .

A) anti –TNF agents

- currently four monoclonal antibodies to TNF are available for treatment of IBD namely infliximab, adalimumab, golimumab and certolizumab .adverse effects include serious infection like sepsis , pneumonia , abscess , cellulitis , acute hepatitis , activation of latent TB, MS may be unmasked in susceptible individuals ,↑ risk of malignancy and development of antibodies against the biological agent (antibodies against the biological agent is decreased by combination with immunomodulating agents)

Scanned with CamScanner

Infliximab for induction of remission is administered IV 5mg/kg at 0, 2, and 6 weeks followed by 8 weekly infusion for maintenance therapy.

B) 2nd line treatment for patients who have not responded to infliximab

The preferred 2nd line therapy for such patients is either anti-IL -12/23 antibody like ustekinumab (5-7mg/kg state dose subcutaneously) followed by 90mg every 8 weekly) or Janus kinase inhibitors such as Tofacitinib compared to Vedolizumab and adalimumab as 2nd line therapy. Tofacitinib is not indicated for crohn's disease and FDA has issued black box warning about ↑risk of thrombosis and death particularly in RA patients.

C) Severe and Fulminant Colitis

- it is life threatening flare of UC characterized by rapid progression of symptoms over 1-2 weeks
- Toxic megacolon is one of the serious complication of severe colitis (may develop in < 2%)

Management

1) general measures

Admit the patients

- NPO the patient for 24-48 hours
- All drugs that slow the gut motility (like opioids and anti-cholinergic) should be stopped
- All the patients should be given supportive treatment with intravenous fluid to correct dehydration , blood transfusion for significant anemia enteral nutritional support should be provided to malnourished patients
- inflammatory markers along with plain abdominal x-ray and /or CT scan should be order to look for colonic dilatation (>6cm)
- stool examination for clostridium difficile and other bugs
- DVT prophylaxis for all hospitalized patient
- patients with fulminant disease or toxic megacolon who worsen or do not improve within 48-72 hours should undergo surgery to prevent perforation

2) specific measures (stepwise)

- **Corticosteroid** like methylprednisolone 40-60 mg intravenously (higher dose is of no benefit) and hydrocortisone enemas 100mg may be administered twice daily for treatment of urgency or tenesmus. Clinical improvement should occur in 3-5 days in most of the patient (50-75%) and once patient improved oral fluid should be started and IV steroid is switched to oral prednisolone .patients without significant improvement within-5 days of IV steroid should be considered for anti-TNF , cycloserine or should be referred for surgery.
- **Anti-TNF agents** infusion of infliximab(5-10mg/kg) is effective treatment for severe colitis in patients who did not improve within 4-7 days of systemic steroid therapy .furthermore it also lower colectomy rates in severe colitis
- **Cyclosporine** intravenous cyclosporine(2-4mg/kg/day as continuous infusion) is alternative to infliximab and has similar response rates (85%) with cyclosporine and infliximab therapy but associated with higher toxicity (nephrotoxicity , seizures , hypertension and infection)

Scanned with CamScanner

- **Surgical therapy** if patient do not respond to above 3 mentioned medicine then it is unlikely to respond to further medical therapy and therefore surgery is recommended

Name of surgery in toxic megacolon?

25-60% of patients with extensive UC, eventually require surgery

- **Panproctocolectomy with ileostomy**
- **proctocolectomy with ileal-anal pouch anastomosis**
- pouchitis(inflammation in ileal pouch) develops in over 40% of patients within 1 year and up to 80% over the long term , characterized by ↑ stool frequency, faecal urgency ,cramping and bleeding but usually resolves with a 2-weeks course of oral metronidazole 250-500mg 3 times daily) and ciprofloxacin(500mg twice daily)

Surveillance for Colon Cancer

- Surveillance colonoscopies are recommended every 1-2 years in patients with colitis beginning 8 years after diagnosis.
- risk is decreased by long term treatment with 5-ASA and folic acid 1mg/day

Clinical features occurring during the active phase of IBD

- conjunctivitis ,iritis, episcleritis and mouth ulcers
- fatty liver
- liver abscess /portal pyaemia
- mesenteric or portal vein thrombosis
- venous thrombosis
- large-joint arthritis
- erythema nodosum
- pyoderma gangrenosum

Clinical features unrelated to inflammatory bowel disease

- autoimmune hepatitis
- primary scleroing cholangitis and Cholangiocarcinoma(**UC**)
- gall stones
- metabolic bone disease
- oxalate calculi and amyloidosis
- sacroillitis/Ankylosing spondylitis (crohn's with HLA-B27)

Scanned with CamScanner

Truelove-Witts criteria

Assessment of disease severity in ulcerative colitis			
	Mild	Moderate	Severe
Daily bowel frequency	<4	4-6	≥6*
Blood in stools	+/-	+/++	+++
Stool volume	<200 g/24hrs	200-400g/24hrs	≥400 g/24hrs
Pulse	<90 beats/min	<90 beats /min	≥90beats /min
Temperature	Normal	Normal	≥37.8®c*
Hemoglobin	Normal	Normal	<100 g/l (<10 g/l)*
Erythrocyte sedimentation rate	Normal	Normal	<30 mm/h*(or equivalent c- reactive protein)
Serum albumin	>35 g/l (>3.5g/dl)		<30 g/l (<3g/l)
Abdominal x-ray	Normal	Normal	Dilated bowel , mucosal island , thumb –printing of mucosa, absence of features
Sigmoidoscopy	Normal or erythema /granular mucosa		Severe mucosal inflammatory changes ; ulceration ;blood in lumen

The truelove –Witts criteria for acute server ulcerative colitis are ≥6 bloody stools 2/4 hrs plus one or more of :anemia ,fever, tachycardia and high inflammatory makers

Crohn's Disease

- 1/3rd of the cases involve the small bowel most commonly terminal ileum while half of all cases involves both small bowel and colon and again most commonly the terminal ileum and adjacent proximal ascending colon (ileocolitis) so the sites most commonly involved are, in order of frequency, the terminal ileum and right side of the colon, colon alone, terminal ileum alone, ileum and jejunum.
- 1/3rd of the cases have associated perianal involvement in the form of fistulas , fissures and abscess

Scanned with CamScanner

- cigarette smoking is strongly associated with development of crohn's disease and NSAID is a risk factor for flare
- crohn's colitis present in an identical manner to UC but rectal sparing and the presence of perianal disease are features that favors a diagnosis of crohn's disease
- in 10% of cases , it may be difficult to distinguish ulcerative colitis from crohn's disease and granulomas on biopsy are present in less than 25% of patients but are highly suggestive of Crohn's disease

Treatment of active Disease

- crohn's disease is a chronic lifelong disease with exacerbation and remission periods .as there is no specific therapy exist , therefore the aim of treatment is symptomatic improvement and control of the disease to improve quality of life , reduce disease progression and complication

Poor prognostic factors of crohn's disease

1) onset at young age
2) high inflammatory markers (↑CRP and low albumin etc
3) deep ulceration on endoscopy

A) Mild/Low Risk disease

1) Terminal Ileum Or Ascending Colon Disease

- Budesonide 9mg (extended –release) once daily for 8 weeks. once remission is achieved , budesonide is tapered over 2-4 weeks
- 5-ASA is often prescribe (melamine 2.4-4.8) ,however there is clinical trial data supporting their efficacy

2) Left-Sided Or Diffuse Colitis

- oral corticosteroid like prednisolone 40mg once daily for 1-2 weeks and once disease is under control , the dose is tapered over gradually over 4-8 weeks
- Sulfasalazine (1.5-3g) twice daily is an effective treatment involving the colon (not small intestine). if patient responded to the drug , it can be continue for maintenance therapy .however , due to potential adverse effects, alternative others oral 5-ASA agents that release throughout the colon like delayed-release mesalamine and balasalazide(2.25 g TDS)
- apart from pharmacological therapy , patient is advised a well-balanced diet with minimal possible restriction .eating smaller but more frequent food is recommended
- loperamide may be given for diarrhea

B) Moderate to Severe /High –Risk Cohn Disease

1)

- In this scenario corticosteroid is again 1st line therapy for induction of remission. oral corticosteroid 40mg/day for 1-2 weeks followed by tapering over 4-8 weeks and in case of indoor patient methylprednisolone(40-60mg IV)

Scanned with CamScanner

- it is recommended in most patients that a biological agent should be started when corticosteroid is taper .in case where biological agent is not initiated for whatsoever reason , then long term treatment with immunomodulators (azathioprine and methotrexate) should be started as steroid –sparing maintenance therapy

2) Biologic Therapies

- Induction therapy with a biological agent is recommended with for almost all patients with moderate to severe crohn's and those who have a good response to treatment should be maintained on long-term remission therapy. Treatment options include anti-TNF, anti-integrin and anti-IL 12/23. The choices of biological agents depend on the disease severity, patient's age, comorbidities, patient's preference and drug cost.

A) anti-TNF therapy

- For moderate to severe disease, two anti-TNF agent infliximab (5mg/kg at 0 , 2, and 6 weeks)and adalimumab are recommended as the preferred first-line agents, for induction of remission. 2/3rd of patients have significant improvements in symptoms. furthermore , combination of anti-TNF agent with an immunomodulators archive higher rates of clinical and mucosal improvement but at the cost of significant adverse effect like myelosuppression
- there is high –risk of relapse in most of the patients (80%) within one year in the absence of maintenance therapy. therefore , maintenance therapy of infliximab(5mg/kg every 8 weekly) and or adalimumab (40mg SC every 1-2 weekly) is recommended

B) Anti-integrins therapy (Recent Advances)

- vedolizumab is 1st line agent for induction of remission , in severe crohn's disease , where anti-TNF is not indicated for whatsoever reasons .Additionally , it is used as 2nd or 3rd line agent in patients who have not responded or lost response to anti-TNF agents or ustekinumab

C) Anti-IL 12/IL-23 antibody (Recent Advances)

- Ustekinumab is indicated for severe crohn's disease where conventional therapy fail to achieve remission or not indicated for whatsoever reasons .Additionally , may be used 1st line as well

Indication of surgery in crohn's Disease

- resistance to maximum tolerated medical therapy
- intra-abdominal abscess
- massive –bleeding
- fistulas(**pelvic-MRI** → anti-TNF has excellent role ± surgery)
- intestinal obstruction

Surveillance Colonoscopy in crohn's

- ≥ 8 years of the disease , the annual colonoscopy is recommended due to ↑ risk of lymphoma and small intestine adenocarcinoma

Colorectal Cancer (CRC)

Scanned with CamScanner

CARE of CA Colon

- patient denied HX of obesity and sedentary life style
- there is no HX of smoking , chronic alcohol intake(weakly associated) and family HX of GI malignancy
- **there is HX of ↓ fibers intake and ↑ dietary intake of red meat**
- there is no HX of radiation exposure and polypharmacy
- there is no HX of gut pathology like IBD
- there is HX of polyps (**goshat ka tukra)** in colon (**anorectal adenomas**)
- there is no HX of visual abnormality , widening of teeth , snoring at night and pads like enlarged hands (**acromegaly**)

- **ask Complication due to metastases from head to toe**

- ask about common complication like anemia , intestinal obstruction and ascites

Investigations

- CBC→ anemia
- faecal occult blood (FOB)
- faecal immunohistochemistry testing (FIT)with faecal multitarget DNA assay is superior than faecal occult blood
- LFT →obstructive jaundice due to PSC or metastatic disease
- **CEA**→ it is of limited importance in diagnosis , since values are normal in many patients , but CEA testing can be helpful during follow-up to monitor for recurrence
- **ultrasound abdomen** →for detection of mass and metastatic liver disease
- **Colonoscopy** →investigation of choice and permit biopsy for pathological confirmation
- **CT Colonoscopy** →this is sensitive and non –invasive technique for diagnosing tumors and polyps of more than 6mm diameter.
- once the diagnosis of CA Colon has been made , CT(contrast) of the chest , abdomen and pelvis should be performed as a staging investigation , particularly to detect hepatic metastases
- **pelvic MRI or endorecatl ultrasound /colonoscopy** should be used for local staging of rectal cancer

- **Omega 3 fatty acid and aspirin has protective role against CA-Colon**

Management

Surgical resection

- minimally invasive , laparoscopically assisted colectomy is similar to open colectomy in outcomes and recurrence of the disease
- surgical resection (with lymph node biopsy) of the colonic tumor is the treatment of choice for almost all patient

Scanned with CamScanner

- it may be curative in patients with stage I ,II and III disease and even some patient with metastatic(stage IV) disease
- following surgical resection , **chemotherapy has been demonstrated to improve overall and tumor-free survival in selected patients** with colon cancer depending on the stage

A) Stage I

- no adjuvant therapy is recommended for stage 1 colon cancer , due to the excellent 5-year survival rate (92%) with colectomy

B) Stage II(node-negative disease)

- significant survival in stage II from adjuvant chemotherapy has not been demonstrated .However , healthy patient with stage II who are at higher risk for recurrence(perforation, obstruction , poorly differentiated poorly pathology ,lymphatic or vascular) may benefit from adjuvant chemotherapy

C) Stage III(node-positive disease)

- In stage iii, with surgical resection alone, the expected 5-year survival rate is 30-50%. Postoperative adjuvant chemotherapy (for 6months) significantly increases the disease –free survival as well as overall survival by up to 30% and therefore, recommended in all fit patients.

Chemotherapy Regimens

A) FOLFOX regimen

- in consist of oxaliplatin , 5-flurouracil , leucovorin and (± bevacizumab or cetuximab)
- it is better regimen with 5-year survival 73%

B) FOLFIRI regimen

- Consist of irinotecan, 5-flurouracil and folinic acid
- (5-year survival 67%)

D) Stage IV (metastatic disease)

- the primary goal is to slow the progression of the disease while maintaining a reasonable quality of life
- a subset of these patients has limited disease that is potentially curable with surgical resection like resection of isolated liver metastases and resection or radiation of isolated pulmonary metastases
- CA arises from the left sided colon has longer survival compare from right sided colon
- patients with unresectable metastatic disease should undergo local ablative techniques
- currently **FOLFLOX** and **FOLFIRI** is the preferred first line treatment .Additionally , addition of a biological agent(Bevacizumab) to the above mentioned regimens increases response rates and overall survival

Scanned with CamScanner

- for patient with **positive K-ras wild type mutation** , the cetuximab and panitumumab(**monoclonal antibodies targeting EGFR (Recent Advances)** should be added in metastatic colorectal cancer

Follow-Up after surgery of colorectal cancer

- the majority of the colorectal cancer recurrence occours within 3 years of completion of treatment and almost all(90%) occours within 5-year
- patients should be evaluated every 3-6 months for 2 years and then 6 monthly for 5-years with proper HX , examination and laboratory surveillance
- CEA level if baseline levels were elevated
- contrast CT chest , abdomen and pelvis every 6-12 months for 5 years
- colonoscopy 1 year after resection and if there is no polyps detected after 1- year then colonoscopy should be every 3-5 years as surveillance

Prognosis

- depend on stage of the disease and for each stage **rectal cancer** have worst prognosis
- 5- year survival of stage I is 90% , stage II is 70-85% , stage III with less than 4 lymph nodes 67% and more than 4 nodes involved is 33% and stage IV is 5-7%

Modified Amsterdam Criteria for Hereditary Non-Polyposis Colon Cancer

- three or more relatives with colon cancer (at least one first-degree)
- Colorectal cancer in two or more generation
- At least one member affected before 50 years of age
- familial adenomatous polyposis excluded

A) Familial adenomatous polyposis

- it is autosomal dominant disorder accounting for 1% of colorectal cancer
- it result from germ line mutation of a tumor suppresser gene called APC gene on chromosome 5
- around 20% of cases arise as new mutation and have no family history
- it is characterized by hundreds to thousands of adenomatous colonic polyps develop in 80% of patients by age 15 and later on per rectal bleed may occur
- In those affected, cancer will be developing within 10-15 years of the appearance of adenoma and almost 90% will develop colorectal cancer by the age of 50 years.
- there may be non-malignant polyps in the stomach and duodenal adenomas are also found in most of the cases where malignant transformation may occours and is the leading cause of death in those who have had prophylactic colectomy
- early identification of affected individuals before symptoms is essential and diagnosis is excluded if sigmoidoscopy is normal and newly diagnosed cases should undergo for genetic testing for confirmation of the diagnosis including first degree relatives .However , despite surveillance , approximately 1 in 4 patients with FAP have cancer by the time they undergo colectomy

Scanned with CamScanner

Extra –intestinal features of familial adenomatous polyposis
• Congenital hypertrophy of the retinal pigment epithelium (70-80%)
• Epidermoid cysts (extremities, face, scalp) (50%)
• Benign osteomas, especially skull and angle of mandible (50-90%)
• Dental abnormalities (15-25)[8]
• Desmoids tumours (10-15%)
• Other malignancies (brain, thyroid, liver, 1-3%)
• Gardner 's syndrome

Variants

i) Turcot's syndrome

- FAP with primary CNS tumours like astrocytoma or medulloblastoma and congenital hypertrophy of the retinal pigment epithelium (CHRPE)

ii) Gardner syndrome

- FAP with benign osteomas especially skull and angle of mandible , epidermoid cyst (involving face , extremities & scalp) and dental abnormalities

iii) Cowden syndrome

- FAP with fibrocystic disease , breast cancer and thyroid cancer

Treatment

- treatment of choice is total proctocolectomy with ileal pouch-anal anastomosis
- periodic surveillance OGD every 1-3 years is recommended to detect and monitor duodenal and periampullary adenomas

B) Juvenile polyposis

- In Juvenile polyposis, tens to hundreds of mucous –filled hamartumatous polyps in the colorectum. criteria for diagnosis include
  - i) ten or more colonic juvenile polyps
  - ii) juvenile polyps elsewhere in the gut or
  - iii) Any polyps in those with a family history.
- One –third of cases are inherited as autosomal dominant and on-fifth develops colorectal cancer before the age of 40.

Scanned with CamScanner

- colonoscopy with polypectomy should be performed every 1-3 years and colectomy considered for extensive involvement

C) Peutz-Jeghers Syndrome

- an autosomal dominant disorder characterized by multiple hamartomatous polyps in the small intestine and colon along with pigmentation of the lips ,mouth and digits
- Clinically, it may be asymptomatic or there may be chronic per rectal bleeding. anemia and intussusception can occur.
- There is a significant risk of small bowel or colonic adenocarcinoma and ↑ risk of cancer of ovary, testis, ovary, breast and endometrium.
- testicular examination is essential for men , while women should undergo pelvic examination , cervical smears and regular mammography
- first degree relative should also undergo screening

Diagnostic criteria

- Diagnosis requires two of the three following features
  - i) small bowel polyposis
  - ii) mucocutaneous pigmentation
  - iii) family history suggestive of autosomal dominant inheritance

Treatment

- affected people should undergo regular upper endoscopy ,colonoscopy and small bowel and pancreatic imaging
- polyps greater than 1 cm in size should be removed

Scanned with CamScanner

APPROACH TO CHRONIC DIARRHEA (AS A CASE OF HIV)

P/C

Loose motions -6months

(HOPI)ODPARA

Patient, who is normotensive and normoglycemic presented with loose stools for the last 6 months. According to the patient it was of gradual onset, episodic and progressive in nature. Patient, initially, experienced **5-6 episodes** of **large volume** brown **color** stools that was watery in **consistency** but for the last one month patient experienced 10-15 episodes in 24 hours including 2-3 episodes at **night** time .it is not exacerbated with eating certain kind of food like wheat or milk and not relived with **fasting**. It is associated with 5KG weight loss; however there is no HX of any **blood or mucus** in the stool and Hx of urgency or sensation of incomplete evacuation. However, there is no HX of .....

DDs of Small bowel diarrhea (signify by large –volume, watery stool, abdominal bloating, cramping mid-abdominal pain and there is no blood or mucus)

1) **Malabsorption** (signify by Bulky , pale ,weight loss , nutritional disturbance and offensive stools that float in the toilet signify malabsorption)
   - A) **Lactose Intolerance** there is no HX of abdominal bloating and worsening of loose motion following intake of milk or dairy products
   - B) **celiac disease** there is no HX of growth retardation and pruritic skin lesion on body particularly elbows and knees
   - C) **Whipple Disease** there is no HX of joint pain , shortness of SOB & pedal edema and memory loss associated with these symptoms
   - D) **lymphoma** there is no Hx of night sweats , heaviness in abdomen and palpable lymph nodes
2) **TB** there is no past or contact HX of TB , low grade fever with night time sweating
3) **IBD** there is no HX of oral ulceration , joint pain , skin rash ,red eyes and painful skin nodules
4) **Scleroderma** there is no HX of skin tightening, difficulty opening of mouth and shortness of breath associated with these symptoms
5) **chronic pancreatitis** there is no HX of gall stones ,chronic epigastric pain radiating to back
6) **Giardiasis** there is no HX of recent travel and excessive abdominal flatulence
7) **Endocrine causes**

- **Hyperthyroidism** → there is no HX of heart intolerance , tremors of hands and increased heart beats
- **Carcinoid syndrome** →there is no HX of facial flushing and wheezy chest
- **Zollinger Ellison syndrome** →chronic epigastric pain not reliving with proton pump inhibitors and associated with blood in vomitus or black color stools
- **Pheochromocytoma** → there is no HX of episodic headache , sweating and extreme ↑ BP

Scanned with CamScanner

- **Diabetes Mellitus as autonomic neuropathy** → there is no HX of polyuria , polydipsia and dizziness on standing from sitting position
- **Addison Disease** → there is no HX of darkening of skin , abdominal pain and dizziness on standing from sitting position

DDS of Large Bowel Diarrhea (signify by small quantity, blood or mucus in the stool, cramping lower abdominal pain urgency or tenesmus)

1) **HIV** → there is significant HX of high risk sexual behaviour
2) **GI malignancy** →there is no HX of decreased appetite and lumps & bumps in the body
3) **Chemo/Radiation enteritis** →there is no HX of exposure to radiation for whatever reason
4) **over the counter laxative**
5) **medication/antibiotic induced diarrhea**→ there is no HX of prolong antibiotic use **or** drugs like thyroxin or colchicine etc
6) **ischemic colitis** →there is no HX of DM , HTN or ischemic heart disease and pain in the abdomen after meals

DDs of mixed diarrhea (having features of small & large bowel diarrhea)

1) HIV
2) TB
3) IBD

exclude only few relevant important DDs

CARE of (HIV) chronic Diarrhea

- there is significant HX of high-risk sexual behaviour including homosexuality and IV drug abuse(so here it is most likely HIV induced diarrhea , therefore I would skip the risk factors and etiologies of other causes of chronic diarrhea)

Complications (of diarrhea and the primary cause)

A) Complications of Diarrhea

- weight loss
- paleness of complexion due to ↓ iron , folic acid and B_{12}
- night blindness →**vitamin A**
- Hair loss , oral ulcer and perioral lesion→ **vitamin B complex**
- poor wound healing and gums bleeding → **protein, vitamin C & zinc**
- bones pain and difficulty rising from sitting position (proximal myopathy)→ **vitamin D**
- easy brusibility , bleeding from body orifices → **Vitamin K**
- **↓ bulk of muscles and body swelling→↓ protein**
- HX of fits, drowsiness or muscles weakness→ **serum electrolytes disturbance**
- HX of tingling , paresthesia and numbness → **peripheral neuropathy ↓ B12**

B) Complications of the diagnosis e.g. primary cause like HIV here

- **CNS**→ Depression , fits and altered sensorium
- **EYES** →redness and ↓ vision
- **Oral cavity** → ulcerations
- **Skin** → rash , papules and painful skin nodules

Scanned with CamScanner

- **RESP**→ SOB , cough ,hemoptysis and TB
- **CVS** →infective endocarditis , LVF(SOB & orthopnea)
- **Renal** → frothy urine ,periorbital puffiness and body swelling(Nephrotic due to FSGN)
- **Adrenal gland** → darkening of skin , dizziness on standing from sitting position
- **abdomen** →Hepatosplenomegaly
- **Spinal cord**→ BL lower limb weakness, neuropathy. myopathy and bowel and bladder involvement
- **Blood** →pancytopenia and lymphoma(lumps & bumps in the body)
- **complication of ART → like** anemia blackening of nails , weight gain , deranged glycemic control & lipid profile , neuropathy and pancreatitis

ITP of chronic diarrhea (ask about specific investigations, treatment and procedures)

Examination

Apart from standard examination you must check

- you must listen to bowel sounds for at least 30 seconds to one minutes
- checking orthostatic BP is must
- it is compulsory to look for signs of dehydration and malabsorption
- ask permission for genital and rectal examination
- cranial nerves examination in case of suspected HIV & TB
- In Fundaoscopy look for CMV retinitis and choroid tubercles
- GAIT examination along with height and weight

ASK Relevant

PAM-HUG-FOSS-TV-F

So based on Hx and clinical examination my clinical diagnosis or differential diagnosis are

1) HIV
2) Abdominal TB
3) Lymphoma

Scanned with CamScanner

VIVA OF CHRONIC DIARRHEA

What is osmotic and secretory diarrhea?

- the stool osmolality may be estimated by multiplying the stool (Na + K)× 2 .the osmotic gap is the difference between the measured osmolality of the stool(or serum) and the estimated stool osmolality and normally less than 50 while increased osmatic gap **signify osmotic diarrhea** which are commonly due to malabsorption , laxative abuse and carbohydrate malabsorption (lactose, fructose and sorbitol)
- **Secretory diarrhea** is due to ↑ intestinal secretion or ↓ absorption that is characterized by high volume diarrhea with normal osmatic gap and that is little or no influenced by fasting. It is due to endocrine tumors that stimulate pancreatic or intestinal secretion like(VIPoma, Carcinoid and Zollinger –Ellison syndrome) , bile salt malabsorption and microscopic colitis

How will you investigate this patient?

- **CBC** →anemia may be micro or macro and or mixed
- **Serum electrolyte**→ ↓ Na or K
- **LFTs serum Albumin** ↓
- **PT,APTT& INR** → deranged ↑
- **ESR/CRP**→ may be raised
- **stool** microscopy & routine examination

Specific

- **TFTs**
- **anti-TTG** (IgG& IgA)
- **stool examination** for ova , cyst ,WBC , fat calculation (Sudan stain and positive stain signify malabsorption) calprotectin and multiplex PCR assay
- **stool elastase** (<100mcg/g) level may suggest pancreatic insufficiency
- **faecal calprotectin or lactoferrin** ↑ level may suggest IBD
- **quantification of the stool**→ 200-300 g/24 hours may suggest a functional disorder like IBS while ≥.5kg/24 hours may suggest secretory diarrhea
- **colonoscopy with biopsy** →may help in diagnosis of IBD, microscopic colitis ,colonic neoplasia and in case of HIV specific pathogen like cryptosporidium ,microspordia and M-avium complex
- **OGD**→ in case of small intestine pathology like celiac disease and whipple disease
- **CT-abdomen and endoscopic ultrasound** → Calcification may suggest chronic pancreatitis (insufficiency) while Ileal thickening may be either suggestive of TB , lymphoma and crohn's (Non-caseating granuloma, skip lesion and thickness on one side is in favor of crohn's)
- **CT/MRI enterography** → may detect small bowel lymphoma , carcinoid and jejunal diverticula as cause of chronic diarrhea

Scanned with CamScanner

- **^{75}SeHCAT test**→ retention of less than 11% at 7th day if intravenous 75Se-homotaurocholate on scintigraphy ,is suggestive of bile salt malabsorption
- **Somatostatin receptor scintigraphy**→ may localized neuroendocrine tumor
- **serologic tests for neuroendocrine tumors**
- medullary thyroid carcinoma →Calcitonin
- Zollinger –Ellison Syndrome → gastrin
- carcinoid →urinary 5-HIAA
- VIPoma→VIP
- **breath test**→ bacterial over growth (less specific)
- **HIV related tests**(see below for detail discussion)

It was a general approach how to investigate the chronic diarrhea now we ll discuss the major and important (**possible long cases in exam**) causes of chronic diarrhea one by one.

1) Coeliac Disease

- strong association with HLA-DQ_2/DQ_8
- It can present at any age but in adult usually during 3rd or 4th decades and female are affected twice
- symptomatology and severity depend on extend of small bowel involvement
- Dermatitis herpetiformis is characteristic skin rash consisting of pruritic papulovesicles over the extensor surface of elbows , knees, buttocks ,trunk , scalp and neck .it occours in less than **10% of patients** of coeliac disease
- unrecognized coeliac disease is associated with mild-under nutrition and osteoporosis

Specific Investigation

- **anti-TTG (tissue transglutaminase) IgA& IgG** →98% specific and sensitive and is 1st line screening test
- **anti-endomysial antibodies IgA& IgG** → 85-95 %sensitive and approximately 99% specific for the diagnosis(except in the very young infant)
- **anti deamidated gliadin peptide (anti-DGP)** →has also excellent sensitivity and specificity
- **OGD with small bowel biopsy** →as the histological changes may be patchy , therefore more than 4 biopsies from the 2nd part of duodenum and one from the duodenal bulb (proximal part) should be taken .histological features include blunting or complete loss of intestinal villi , hypertrophy of the intestinal crypts and intraepithelial lymphocytosis .some time villi appear normal but there are excess numbers of intra-epithelial lymphocytes **(lymphocytes duodenosis)**
- **What are the other causes of subtotal villous atrophy?**

1) tropical sprue(2)lymphoma (3) HIV-related enteropathy (4)Giardiasis(5)whipple disease (6) radiation(7)Zollinger-Elisions syndrome and hypogammaglobulinemia

- **Dexa-Scan**→ for detection of osteoporosis

Scanned with CamScanner

- **CBC with peripheral smear**→ anemia (micro/macro or mixed)and features of hyposplensim like targets cells ,spherocytes and Howell-Jolly bodies
- **Workup for other autoimmune disorders** → strongly association type 1 diabetes (2-8%) and thyroid disease (5%) etc.

Treatment

- **Gluten free** (wheat, rye barely and initially oat) diet is the mainstay of treatment .improvement in symptoms should be evident within few weeks after gluten free diet. The most common cause of treatment failure is incomplete removal of gluten from the diet. Flare due to intentional or unintentional reintroduction of gluten diet should treated with steroid (prednisolone 40mg) for 2 weeks while gluten –free diet is reinitiated.
- there remain a small number of patient who fail to respond adequately to gluten free diet and they require therapy with steroids or immunosuppressive therapy
- level of all antibodies became undetectable after 3-24 months of dietary gluten withdrawal and may be used to monitor dietary compliance particularly in those whose symptoms fail to resolve after gluten free diet
- Dapson when dermatitis herpetiformis is not responding to gluten free diet
- correction of existing deficiencies via supplements
- most patient with coeliac disease have temporarily or permanently lactose intolerance ,and therefore should avoid dairy product until the symptoms have improved on the gluten –free diet
- treatment of osteoporosis with calcium , vitamin D and bisphosphonate therapy

Complications

- there is twofold increased risk of enteropathy associated T- cell lymphoma , small bowel carcinoma and squamous cell carcinoma of the esophagus
- osteoporosis & osteomalacia
- In few patient **ulcerative jejuno-ileitis** may develop characterized by fever, pain, obstruction or perforation. diagnosis is made by barium studies or enteroscopy but sometime laparotomy with full biopsy may be needed .glucocorticoids are used with variable success and some patients may require surgical resection and parenteral nutrition

Prognosis

- prognosis is excellent with less than 5% cases are refractory

2) Whipple Disease (it is very rare disease but examiner may ask major points in viva)

- causative organisms is **tropheryma whipplei** but source of infection is unknown and no human to human spread is documented
- Multisystem illness characterized by fever, lymphadenopathy, arthralgia, weight loss and chronic diarrhea etc.
- Extra-intestinal feature of Whippple's disease include seronegative nondeforming large joint arthritis , heart block ,endocarditis, dementia , myoclonus ,fits & ataxia, pulmonary infiltrates, pleurisy& cough , anemia , lymphadenopathy and pigmentation

Scanned with CamScanner

- Involvement of system in descending order GI →MSK→Haematological→ Neurological →pulmonary and cardiac.

Specific investigation

- Endoscopic biopsy of the duodenum where lamina propria with PAS-positive macrophages containing gram positive bacilli and dilation of the lacteal
- 90% cases are diagnosed by the above method while rests of the cases are diagnosed by T whipplei –specific PCR of CSF and tissue. PCR is 97% sensitive and 100 specific

Treatment

Patient responds well to antibiotic therapy within weeks and complete clinical response may occur within 1-3 months but relapse may occur in up to $1/3^{rd}$ of patients after discontinuation of treatment .therefore, prolong treatment for at least 1 year is required

- ceftriaxone 1g IV BD for 2 week or
- meropenem 1g IV BD for 2 weeks followed by tab Septran DS (160/800 mg) BD for one year

Monitoring of RX

Biopsy of duodenum or PCR of CSF 6 monthly to one year should be done and absence of PAS or negative PCR predict low -risk of relapse .relapse may be treated similarly or alternative regimen of doxycycline and hydroxychloroquine

2) Small Bowel Bacterial overgrowth

- it is also called blind loop syndrome
- normally duodenum and jejunum contain fewer than 10^4/mL organism which are usually derived from saliva
- in bacterial overgrowth , there may be 10^8-10^{10}/mL organisms , most of which are normally found only in colon
- There are many factors that impair the normal physiological mechanisms controlling bacterial proliferation and hence predispose to bacterial overgrowth, the most important are loss of gastric acidity (long-term PPI, partial gastrectomy) impaired intestinal motility (systemic sclerosis, DM) and structural abnormalities (strictures and surgery etc.).

Investigations

- **Hydrogen breath test (or methane breath test)**
  in this test patient ingest glucose 75 g or lactulose 10g and if bacteria is present within small bowel ,they rapidly metabolized the glucose or methane and if there is rise in exhaled breath hydrogen of ≥20 ppm or methane of≥ 10 ppm within 90 minutes ,is suggestive of bacterial overgrowth .it has 65% diagnostic accuracy
- **aspirate and culture** of distal **duodenal secretion** that demonstrate over 10^3 organisms/ml. it is confirmatory test but invasive
- **CT/MR enterography /barium studies**→ to look for mechanical factors predisposing to intestinal stasis

Scanned with CamScanner

- **low serum level of B12 , with normal or elevated level of folic acid because the bacteria produces folic acid** ,it's also suggestive of bacterial overgrowth

Treatment

- treat the predisposing factors , where possible
- treatment with broad antibiotics for 7-10 days improves symptoms in up to 90% of patients for weeks to months
- there is no drug of choice
- recommended regimens includes rifaximin 550mg three times daily ,ciprofloxacin 500mg BD ,norfloxacin 400mg BD and combination of neomycin 500mg BD & metronidazole 250mg TDS.

3) Lactase Deficiency (Lactose Intolerance)

- Human milk contains around 200 mmol/L(68 g/L) of lactose which is normally digested to glucose & galactose by the brush border enzyme **lactase** before absorption
- in primary lactase deficiency, the jejunal morphology is normal .secondary lactase deficiency occours as a consequence of disorders that damage the jejunal mucosa like coeliac disease, giardiasis, viral gastroenteritis ,short bowel syndrome and crohn's disease
- symptoms are not specific and depend on the severity of lactase deficiency and the amount of lactose ingested
- symptoms may mimics IBS but the correct diagnosis is suggested by clinical improvement on lactose withdrawal

Investigation

- **Hydrogen breath test**

  After ingestion of 50g of lactose, a rise in breath hydrogen of more than 20ppm within 90 minutes is considered a positive test

Treatment

- Dietary exclusion of lactase is recommended, although most patients are able to tolerate small amount of milk without symptoms.
- most patient with lactose intolerance, can drink at least one cup of daily milk(12g of lactose) without symptoms and while with higher doses of ingestion, an osmotic diarrhea may occours
- most food markets provides milk that has been pretreated with lactase
- Calcium supplement should be advised to the patient who choose to restrict or eliminate milk or milk product , to reduce the risk of osteomalacia &osteoporosis

4) Zollinger –Ellison Syndrome (ZES)

- Gastrinomas are one of the several gut neuroendocrine tumors having similar histopathological features .these includes **ZES,** carcinoid, insulinoma and VIPoma.
- it is a triad of severe peptic ulceration , gastric acid hyper secretion and a neuro-endocrine tumour of the pancreas and (45%)duodenum(gastrinoma)
- most cases are sporadic and 25% are associated with multiple endocrine neoplasia 1(MEN1)

Scanned with CamScanner

- presented with severe and multiple ulcers in unusual sites , such as the distal duodenum , jejunum or esophagus that is refractory to standard ulcer treatment and accompanied by diarrhea in one 3rd patients
- the acid secretion is may be so elevated that it reaches the upper small intestine and reducing the luminal PH to 2 or less that causes pancreatic Lipase inactivation and precipitation of bile acids that ultimately result in diarrhea
- almost one-half to two-thirds are malignant but are often slow-growing

Investigation

- patient with a serum gastrin level of greater than 1000pg/mL and acid hyper secretion almost established the diagnosis
- in case of lower gastrin (and acid level), a **secretin stimulation** should be performed to differentiate between **Zollinger –Ellison** from other causes of **hypergastrinemia**(like hypochlrohydria with increased gastric PH) .in this test intravenous secretin (2units/kg) result in paradoxical and dramatic increase (200ng/L) in gastrin within 2-30 minutes in majority of patients (85%) with gastrinoma
- to exclude MEN1 in gastrinoma patient and family , serum calcium ,PTH , LH-FSH, growth hormone and prolactin should be advised

Tests for localization

- **Somatostatin receptor scintigraphy (SRS) with single photon emission computed tomography (SPECT)**

As gastrinoma express Somatostatin receptors that bind radiolabelled Octreotide and by this way we detect gastrinoma in pancreas, lymph nodes, unusual body sites and metastatic lesions in bones and liver

- ^{68}**gallium DOTATATE PET scan** for tumor detection and staging
- in case where SRS is negative , tumors localization is best achieved by endoscopic ultrasonography **(EUS) and CT**

Treatment

A) **Localized Disease**

- symptomatic treatment with proton pump inhibitors (**double than** normal dose may be required)
- cure can be achieve if surgical resection is done before hepatic metastases
- lymph node metastases does not adversely affect prognosis
- in MEN1 , due to the presence of multifocal tumors and long term survival without intervention , surgery is usually not recommended

B) **Metastatic Disease**

- The most important survival predictor is hepatic metastases
- in metastatic disease , proton pump inhibitors(40-120mg) are given to achieve a basal acid output of less than 10 mEq/h as at this level patient is completely asymptomatic and ulcer heals

Scanned with CamScanner

- Due to slow growing nature of the tumors, patient with hepatic metastases have survival of 10 years.

5) Carcinoid syndrome

- episodes of abdominal pain , diarrhea, bronchospasm and weight loss
- Dry skin and flushing typically affect the upper chest, neck and last from 30 seconds to 30 minutes and may be persist for days. there may be facial telangiectasia and carcinoid induced heart problems (like tricuspid regurgitation , pulmonary stenosis, right ventricular endocardial plaques) leading to heart failure and may also cause int5etsinal obstruction (cecal tumors)
- Pellagra may develop (result from conversion of tryptophan (a precursor of niacin) to serotonin by tumor cells) in carcinoid patients.
- bronchial carcinoid produces symptoms without hepatic metastases while foreguts carcinoid tumors produces symptoms only when have metastasized to the liver while hindgut carcinoids do not cause symptoms(as it rarely produce serotonin)

Investigations

- 24 hours urinary level of 5-hydroxyindoleactic acid (false positive in avocado and pineapple)
- fasting plasma chromogranin A(↑↑) level and serum serotonin level(↑↑)
- ECHO → 2 yearly
- CT/MRI of the abdomen or chest and then 1 yearly
- ultrasound of the abdomen → look for liver metastases
- for **localization** of tumor, same investigations as described for Zollinger-Ellison

Treatment

- bronchodilators for wheeze
- surgical resection where possible is curative
- Somatostatin analogue like Octreotide and lanreotide may alleviate flushing and diarrhea
- interferon and other chemotherapeutic regimen also occasionally reduce tumors growth but have not been shown to increases survival

Recent Advances in carcinoid treatment

→Telotristat (250mgTDS PO) which is serotonin synthesis inhibitor is recently approved for carcinoid syndrome diarrhea that is inadequately controlled with Somatostatin analogue (SSA).it can be used in combination with SSA therapy

6) VIPoma

- patient with VIPoma presented with profuse watery diarrhea, hypokalemia and achlorhydria that is also called Varner-Morrison Syndrome
- stool volume of less than 700mL/day almost exclude the diagnosis as in VIPoma typical stool volumes is more than 3L/day
- to produce the syndromes , the tumour are usually more than 3 cm in diameter
- VIP level are elevated in the range of 250 to 500pg/Mm(normal value is less than 190pg/ml
- for localization of tumors same investigations as described for Zollinger-Elisions above

Treatment

Scanned with CamScanner

- **surgery** is the primary initial treatment for most neuroendocrine tumors
- Somatostatin analogue like Octreotide or lanreotide are effective foe symptoms control. Octreotide subcutaneously 20-30mg are required every 4 weekly
- In patients with extensive liver metastases, **occlusion of the arterial blood** flow by hepatic arterial embolization may control hormones related symptoms.in most cases, the tumors are slowly progressive and may allow a reasonable quality of life for many years.

7) Bile Acid Diarrhea

- unabsorbed bile acid pass into the colon and stimulate water & electrolyte secretion causing diarrhea
- it may be idiopathic(**type 1**) or as a complication of small bowel resection (in crohn's ileal resection) and post cholecystectomy (**type II**)
- it may also be associated with certain condition like microscopic colitis , bacterial overgrowth , chronic pancreatitis ,coeliac disease and diabetes
- If hepatic synthesis of new bile acids cannot keep paces with faecal loss, fat malabsorption occours. Other complications includes gallstones , renal calculi (oxalate) and other nutritional deficiencies depending on the severity

Specific Investigations

- Se^{75}-Homocholic acid taurine(SeHCAT) test
- 7 alpha –hydroxycholestenone is a non-invasive marker of bile acid diarrhea

Treatment

- Acid sequestrant like cholestyramine or colesevelam which binds bile salt in the intestine lumen. Aluminum hydroxide is alternative option

8) Short bowel syndrome (intestinal failure)

It is defined as a reduction in the function of the gut below the minimum necessary for the absorption of the macronutrient and /or water and electrolytes such that intravenous supplementation is required to support health and /or growth.
This term can be used only when there are both

i) a major reduction in absorptive capacity and
ii) an absolute need for intravenous fluid support

For detail discussion (causes, types and management) kindly see a reference book as it is beyond the scope of this book .

9) Intestinal Tuberculosis

- it is caused by mycobacterium tuberculosis and M bovis
- TB can affect any part of the bowel but the most frequent site of involvement is the iloececal region
- Patient may present with wide range of symptoms predominantly chronic abdominal pain, weight loss, diarrhea, mass in the right iliac fossa and acute abdomen (30%)
- active pulmonary TB may be present in less than 50%
- it may develop as primary tuberculosis **after ingestion of raw milk or infected sputum**

Scanned with CamScanner

Investigations

- PPD skin test → may be negative
- ultrasonography/ abdominal CT→may show thickening of the cecum ,iloececal valve, ascites and massive lymphadenopathy
- colonoscopy →may shows ulcers , ulcerated mass and sessile polyps predominantly I the iloececal region
- Barium enema and small bowel enema → may reveal narrowing, shortening and distortion of the bowel particularly iloececal region.
- the **diagnosis is established** by either endoscopic or surgical biopsy that shows AFB , caseating granuloma or positive culture while recently detection of the organism in biopsy specimen by PCR is now the most sensitive means of diagnosis

What are the causes of the right iliac fossa mass?

- iloecal TB
- crohn's disease
- lymphoma
- carcinoma of the cecum
- tuboovrain mass in female
- ameboma and actinomyces

Abdominal tuberculosis includes both intestinal and peritoneal tuberculosis

What is the type of ulcer in iloececal tuberculosis?

In iloececal TB **ulcer is transvers** while in crohn's disease the **ulcer is longitudinal**

What are the types of lesions in iloececal tuberculosis?

i) ulcerative (ii) hypertrophic and (iii) mixed

Complications

- intestinal obstruction , fistula formation , hemorrhage and malabsorption
-

Treatment

- six months of standard therapy is appropriate treatment

10) Inflammatory Bowel disease (IBD)

See per rectal bleed

11) CA Colon

See per rectal bleed

Scanned with CamScanner

HIV Infection and AIDS

- HIV is an enveloped RNA retrovirus from the lentivirus family .after mucosal exposure, the virus is carried through dendritic cells to the lymph nodes where infection becomes established. This is followed by viremia and dissemination to lymphoid organs , which are the main sites of viral replication .HIV infects cells having the CD_4 receptors , these includes, T-helper lymphocytes ,mono-macrophages, dendritic cells and microglial cells in the central nervous system . entery into the cell initiate with binding of gp 120 to the CD_4 receptors which result in a conformational changes in gp120 that allows binding to one of the two chemokines co-receptors (CXCR4or CCR5) .The chemokine co-receptor CCR5 is utilized during the initial infection and later on the virus may use CXCR4 . Those individuals who are homozygous for the CCR5 delta 32 mutation do not express CCR5 on CD_4 cells and are immune to HIV infection. The host immune response to HIV infection is both humoral, with the development of antibodies to a wide range of antigens, and cellular, with proliferation of HIV- specific CD8 cytotoxic T lymphocytes, resulting in a CD8 lymphocytosis and reversal of the usual CD4:CD8 ratio .CD8 cytotoxic T lymphocytes kill activated CD4 cells that are replicating HIV, but not latently infected cells.
- HIV is transmitted by sexual contact, by exposure to blood (occupational exposure in health care worker or IV drug abuser) and blood product, or to infants of HIV-infected mothers. **Worldwide, the major route of HIV transmission is heterosexual and when blood transfusion from an HIV –infected donor occours, the risk of transmission is 95%.** The risk of contracting HIV after exposure to infected body fluid is multifactorial and depends on the integrity of the exposed site, the type and volume of the fluid, and the level of the viremia in the source person.
- **HIV is not transmitted by** respiratory droplets spread, by vectors such as mosquitoes, or by causal nonsexual contact. Saliva, sweats, stool and tears are not considered infectious fluid
- The syndromes or complications caused by HIV infection are due to one of the three main mechanisms

i) immunodeficiency → attack the immune system resulting in weak / and or destroy immune systems
ii) Autoimmunity
iii) Allergic and hyper sensitivity

- A person with positive HIV serology who have ever had a CD4 lymphocyte count below 200 cells/meL or a CD4 percentage below 14% are considered to have AIDS

Scanned with CamScanner

Risk of HIV transmission after single exposure to an HIV infected source	
HIV exposure	approximate risk
Sexual	
Vaginal intercourse female to male	0.05%
Vaginal intercourse male to female	0 .1%
Anal intercourse insertive	0. 05%
Anal intercourse receptive	0. 5%
Oral intercourse insertive	0 .005%
Oral intercourse receptive	0 .01%
Blood exposure	
Blood transfusion	90%
Intravenous drug users sharing needles	0 .67%
Percutaneous needlestick injury	0 .3%
Mucous membrane splash	0.09%
Mother to child	
Vaginal delivery	15%
Breastfeeding (per month)	0.5%

Factor increasing the risk of transmission of HIV	
Common to all transmission categories	
• High viral load	
Sexual transmission	
• STIs, especially genital ulcers • cervical ectopy • Rectal or vaiginal laceration • Menstruation • Uncircumcised male partner	• Receptive anal intercourse • Depot intramuscular progesterone contraceptive use
Injection drug use transmission	
• Sharing equipment • Linked commercial sex • Intravenous use	• Concomitant cocaine use • Incarceration
Occupational transmission	
• Deep injury • Visible blood on device	• Needle was in a blood vessel
Vertical transmission	
• Prolong rupture of membrane s	• Older gestation age

Scanned with CamScanner

How will you investigate this person?

Baseline investigations

- CBC
- LFTS
- RFTS& urinalysis
- anti-HbsAg& hepatitis C antibody
- syphilis serology
- cervical smear in women
- serum cryptococcal antigen (if CD4 < 100)
- tuberculin skin test
- screening of sexually transmitted infections

Specific tests

- **Elisa & Westron Blot are obsolete now**

i) **4th generation HIV antigen/antibody immunoassay (new advances)**

- It detects HIV-1 and HIV-2 antibodies and HIV-1 P24 antigen. If it is positive then advise ↓

ii) **HIV-1/HIV-2 antibody differentiation immunoassay (multispot immunoassay) (new advances)**

- To confirm infection and to distinguish HIV-1 from HIV-2.
- If it is positive than treat (as it is a confirmatory test) the patient but if inconclusive than advise PCR (viral load tests)

iii) **PCR /HIV-1 viral load**

- more than 1000 copies /mL is significant and should be treated .Additionally, **if tests i&ii are negative and PCR is positive** this is indicative of possible acute HIV infection .while combine sensitivity and specificity of **tests i&ii are 100%** for chronic infection

iv) **Absolute CD4 lymphocyte count**

- it determine stage of HIV infection .there is high risk of an AIDS when CD4 count is less than 200cells/mcL in the absence of treatment

v) **CD4 lymphocyte percentage**

- Percentage may be more reliable than CD4 count. when it is less than 14% , there is risk of complications associated with HIV infection

vi) **HIV rapid antibody test**

- It acts as rapid screening test that yield result in 10-20 minutes. sensitivity and specificity for chronic infection are > 99% and positive test may be confirmed through standard testing as described above

Causes of false positive HIV tests

- persons who are reactive on the initial test and then negative on the confirmatory test and have nondetectable viral loads are presumed to have a false positive test

Causes

- influenza vaccination

Scanned with CamScanner

- autoimmune disease & collagen vascular disorder
- pregnancy (cross reaction with alloantibodies)

CD4 count and risk of common HIV- associated diseases	
<500 cell/mm^3	
• tuberculosis • Bacterial pneumonia • Herpes zoster • Oropharyngeal candidiasis • Non-typhoid salmonellosis	• Kaposi's sarcoma • Non-hodgkin lymphoma • HIV –associated idiopathic Thrombocytopenic purpura
<200 cells/mm^3	
• Pneumocystis jiroveci pneumonia • Chronic herpes simplex ulcers • Oesophageal candidiasis • Cystoisospora belli (synlsospora belli) diarrhea	• HIV wasting syndrome • HIV –associated dementia • Peripheral neuropathy • Endemic mycoses
<100 cells /mm	
• Cerebral toxoplasmosis • Cryptococcal meningitis • Cryptosporidiosis and microsporidiosis • Primary CNS lymphoma	• Cytomegalovirus • Disseminated mycobacterium avium complex (MAC) • Progressive multifocal leucoencephalopathy

WHO staging of HIV

- Stage 1 → flu like symptoms and gen lymphadenopathy but CD4 ≥500
- Stage 2→ latent and CD4 count < 500 but > 350
- Stage 3→ moderate disease and CD4 counts is < 350 but > 350
- Stage 4 → severe Disease and CD 4 is < 200

WHO staging is used for low income population while CDC phases of HIV (3 phases) is used in higher income classification

Treatment of HIV & complications

All patients regardless of CD4 count should be treated and CD4 counts should be monitored every 3-6 months in those taking treatment consistently

1) Treatment of systemic complaints

i) anorexia or decreased appetite

Treatment →ART and then introduce megestrol acetate (400-800mg/day in divided dosses) or dronabinol (an anti-emetic agent).in dose of 2.5-5mg TDS.

ii) weight loss and wasting syndrome

Weight loss and wasting due to HIV may be treated effectively with growth hormone and anabolic steroid .growth hormones (0.1mg/kg/day upto 6mg subcutaneously) for 12 weeks result in modest increase in body weight .Additionally, anabolic steroid like testosterone enanthate or testosterone

Scanned with CamScanner

cypionate (100-200mg intramuscularly) every 2-4 weeks is commonly used .furthermore, anabolic steroids are also available in transdermal or gel formulation.

iii) Nausea

Exclude esophageal candidiasis, depression and Addison as cause of nausea and treat them accordingly. Nausea of unclear origin may be treated with antiemetic like ondansetron (8mgTDS), prochlorperazine (10mgTDS) and metoclopramide (10mg TDS)

2 Pulmonary manifestation /complications

i) pneumocystis pneumonia

- It is the most common opportunistic associated with AIDS and is one of AIDS defining event. Due to non –specific symptoms (like dry cough, fever and SOB), diagnosis may be difficult.

Investigations

- **Xary-chest** (cornerstone of diagnosis)→ it may show bilateral interstitial infiltrate spreading out from the hilar region(in 2/3rd of patients) but may be normal initially
- **HRCT**→ may show ground-glass ' interstitial infiltrate and pneumatoceles
- **Wright-Giemsa stain/direct fluorescence antibody test(DFA)** →definitive diagnosis with this stain of induced **sputum** in 50-80% cases (sputum may be induced by having patients inhale an aerosolized solution of 3% saline →next step for sputum negative highly suspicious patients is BAL and this may yield diagnosis in over 95% of cases .
- **Lactate dehydrogenase**→ may be raised in 95% but the specificity is 75%
- **serum beta-glucan** →it is more sensitive and specific than LDH
- **ABGs**→ hypoxemia may be severe, with a po_2 less than 60 mmHg.

Treatment options

- trimethoprim-sulfamethoxazole 800mg/160mg TDS for 21 days .Additionally , corticosteroids therapy (40mg prednisolone BD for 5 days then, 40mg daily for 6-10 days followed by 20mg daily for 11-21 days) has been shown to improve the course in moderate to severe disease (Pao_2 less than 70 mmHg on room air or alveolar-arterial $O_2 \leq 35$mmHg) when administered within 72 hours of the start of treatment
- Pentamidine→3-4mg/kg/day IV for 21 days (but it is **not available in Pakistan)**
- Primaquine 30mg /day orally and clindamycin 600mg TDS for 21 day and steroid when indicated.

ii) Mycobacterium avium complex

- Atypical mycobacteria (**MOT**) can cause pulmonary disease in AIDS patients with or without preexting lung disease when CD4 counts are less than 50 cells/mcL and respond variably to treatment.
- It may grow on culture of sputum specimen (this may differentiate it from typical mycobacteria) and DNA probes allow for presumptive identification usually within days of a positive culture.

Treatment

- Clarithromycin (500mg BD) with ethambutol(15mg/kg/day max upto 1g) and rifabutin (300mg OD)

Scanned with CamScanner

iii) mycobacterium tuberculosis

- pulmonary tuberculosis in patients with mild immune suppression typically presents as in HIV uninfected patients with a chronic illness and apical pulmonary cavities .However In patients with CD4 counts below 200 cells/mm^3 , lower &middle lobe , interstitial and miliary infiltrate are more common along with mediastinal adenoapthy and exrapulmonary involvement
- PPD skin test or interferon gamma release assay (IGRA and including QUANtiFERON &T-SPOT) should be performed in all HIV patient in whom there is suspected tuberculosis ,However , the lower the CD4 cell counts , the greater the likelihood of falsely negative PPD or IGRA

Treatment

- Treatment is similar to the treatment of HIV-uninfected tubercular patients. However, rifabutin may be substituted with rifampicin in patient receiving a boosted protease inhibitor regimen or doltegravir. if rifabutin is not available then , **double dose ritonavir boosted lopinavir** should be offered and ATT should be initiated 6-8 weeks before ART .

iv) HIV &MDR TB

- Multidrug-resistant tuberculosis may arise due to non-compliance and therefore, it is essential that antibiotic sensitivities be performed on all positive cultures and if (MDR) detected patient should receive at least three medications to which the organism is sensitive.
- Bedaqulin has strong interaction with protease inhibitor and therefore, either closely monitoring should be done or replace protease inhibitor with other antiretroviral regimen.

iv) Bacteria

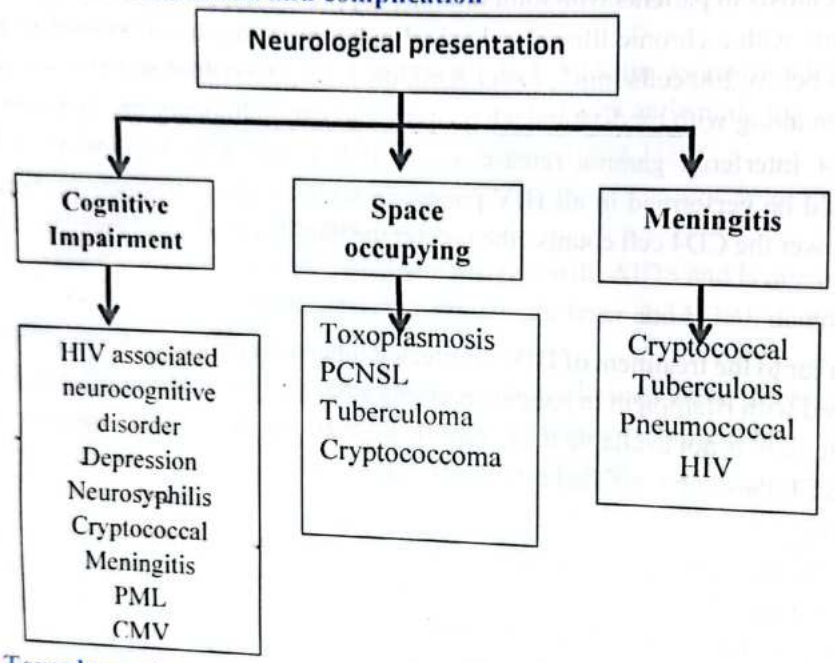
- Community acquired pneumonia is the most common cause of pulmonary disease in HIV – infected person and there is ↑ incidence of infection with pneumococcal pneumonia, Haemophilus influenza and pseudomonas aeruginosa. treatment is similar to HIV-uninfected individuals

v) Viral (COVID-19 & others)

- Patients with HIV on suppressive antiretroviral regimen who contract COVID 19 have a prognosis similar to and can be managed clinically the same as persons who do not have HIV. However, additional caution is warranted for HIV infected persons who develop COVID 19 especially those with poorly controlled HIV or advanced AIDS.
- Isolation of cytomegalovirus from bronchoalvelolar lavage fluid commonly occours in AIDS patients but does not establish a definitive diagnosis.

Scanned with CamScanner

3 →CNS manifestation and complication



1) Toxoplasmosis

- it is most common CNS space –occupying lesion in HIV positive patients and they may presented with headache , focal neurological deficit , seizures and altered mental status

Investigation

- **CD4 counts**→ less than 200 cells/mcL
- **positive serology** →is indicative but does not confirm the diagnosis as many HIV infected patients have detectable titers without having active disease .while conversely , less than 3% of patient with toxoplasmosis have negative serology
- **CT/MRI brain** →multiple contrast-enhancing lesions that tends to be peripheral with a predilection for the basal ganglia
- **definitive diagnosis**→ brain biopsy but this is seldom necessary

Treatment

- Pyrimethamine (2oomg loading followed by 50mg ≤60kg while 75mg for> 60kg) combined with sulfadiazine (1000mg QID for ≤60kg while 1500mg QID for patient weighing > 60 kg) and leucovorin (folinic acid to reduce bone marrow suppression 25-50mg daily) for 6 weeks or until immune reconstitution with antiretroviral treatment occours. Additionally, patient who are intolerant of sulfa who cannot be desensitized, clindamycin 600mg may be substituted with sulfadiazine in the above regimen.
- Moreover, trimethoprim –sulfamethoxazole BD for 6 weeks may also be used as alternative treatment

Scanned with CamScanner

ii) Primary CNS lymphoma (PCNSLs)

- it is high grade B cell non-Hodgkin lymphoma associated with EBV and neuroimaging characteristically shows a single homogenously enhancing periventricular lesion with surrounding edema
- it there is no contraindication to lumbar puncture, PCR for EBV DNA in CSF has a high sensitivity and specificity for PCNSL
- **SPECT** →Positive test is highly suggestive
- brain biopsy is definitive but risky and may be non-diagnostic in upto on-third

Treatment

- Combination chemotherapy like EPOCH (etoposide phosphate, prednisolone, vincristine sulphate (Oncovin), Cyclophosphamide and doxorubicin) with rituximab.
- radiation therapy with dexamethasone for edema and intrathecal methotrexate is alternative treatment options

iii) Cryptococcal meningitis

- it is the most common cause of meningitis in AIDS patients and present with fever and headache while the neck stiffness is present in less than half

Investigations

- **latex agglutination test** → that detect in serum cryptococcal antigen (CRAG) and almost 90% of patient with cryptococcal meningitis have positive CRAG and negative CRAG make this the diagnosis very unlikely
- **Lumbar puncture** →positive culture of CSF for Cryptococcus using Indian ink staining. Furthermore CSF pleocytosis is often mild or even absent and protein & glucose concentration are often variable. Cryptococcal antigen is CSF has high sensitivity and specificity

Treatment

- treatment is divided into three phases , induction , consolidation and maintenance
- **Liposomal amphotericin B** (3-4mg/kg/day intravenously) with **flucytosine** (25mg/kg orally four times daily) for **at least 2 weeks**. It is called induction treatment. In this period there should be clinical improvement and a negative CSF culture on a repeat lumbar puncture. this is followed by **Fluconazole (400mg orally daily)** for at **least 2 months** (called consolidation treatment) and then Fluconazole (200mg daily) for **a minimum of 1 –year duration** (called maintenance treatment).treatment can be stopped after 1 year of maintenance therapy if the patient is asymptomatic and has a load on treatment

iv) Meningococcal meningitis

HIV infected patients are at ↑ risk of meningococcal meningitis and that is why it is recommended for all HIV infected patient aged≥ 2months to vaccinate with meningococcal conjugate vaccine (serogroups A,C W and Y) .

i) stroke

- There is higher incidence of stroke in patient infected with HIV .it may possibly due to either atherosclerosis (accelerated by immune response to HIV), dyslipidemias (caused by some

Scanned with CamScanner

antiretroviral drugs) and HIV vasculopathy. It is worthy to exclude tuberculous meningitis and syphilis in HIV patients presented with stroke.

v) Myelopathy & radiculopathy

- It present with leg weakness with non-sensory level, incontinence and most patients have concomitant HIV-associated dementia (encephalopathy) and you may find spastic Paraparesis and sensory ataxia on examination. In vast majority of patient it is due cored compression from tuberculous spondylitis .MRI spine is normal but it is important to exclude other causes like epidural lymphoma CMV polyradiculopathy and etc. treatment is ART
- **CMV Polyradiculitis** presents with painful legs, progressive flaccid Paraparesis, saddle anesthesia, absent reflexes and sphincters dysfunction. It is diagnosed by lumbar puncture where CSF shows neutrophil pleocytosis (**which is unusual for a viral infection**) and the detection of CMV DNA by PCR confirm the diagnosis.

vi) Peripheral nerve Disease

- HIV infection causes axonal degeneration resulting in sensorimotor neuropathy in about 1/3rd patients. Sensory symptoms predominate It is more commonly occur in old aged and those with lower CD4 counts. Drugs like didanosine and stavudine (NRTIs) can also cause peripheral neuropathy that is more painful and rapidly progressive and it is not always reversible even when the offending agent is discontinued. It is treated with analgesia and analgesic adjuvant and also involve foot care
- Acute inflammatory demyelinating polyneuropathy similar to GBS (except CSF pleocytosis is more prominent than GBS) occours in HIV infected patient. many cases improves with plasmapheresis

vii) Retinitis (Retinopathy)

- most commonly due to CMV and it present with painless and progressive visual loss in severe immune compromised patients .fundaoscopy reveals clear vitreous , however , there may be hemorrhages and exudates in retina often with sheathing of vessels(frosted branch angitis) .it starts unilaterally and if untreated there may be progressive bilateral involvement. there are 3 other conditions that mimic CMV retinitis namely ocular toxoplasmosis (presents typically with a vitritis & retinitis without retinal hemorrhages), HIV retinopathy (a microangipathy that causes cotton wool spots) and Varicella zoster(causes rapidly progressive outer retinal necrosis)
- Diagnosis is clinical, but if there is doubt, detecting of CMV DNA in vitreous fluid is diagnostic.

Treatment

- first line therapy is oral valganciclovir 900 mg BD for 3 weeks followed by 900 mg OD for 3 weeks
- Ganciclovir(10mg/kg/day BD) for 14-21 days and then 5mg/kg daily for same duration
- for sight-threatening infection involving the macula or optic nerve , intravitreal ganciclovir(2mg/injection) or foscarnet(2.4mg/injection) for 1-4 doses/day for 7-10 days

Scanned with CamScanner

- Cidofovir (5mg/kg/week) IV for 2 weeks ,then 5mg/kg every other week with probenecid, 2g orally 3 hours before dose ,1g orally 2 hours after dose , and 1 g orally 8 hours after dose.

4→ Rheumatological Disease

i) arthritis

- HIV can cause a seronegative arthritis, which resembles rheumatoid arthritis and sometime a more benign oligoarthritis may occur.

ii) Diffuse infiltrative lymphocytosis syndrome(DILS)

- It is a benign disorder characterized by infiltration of tissues by CD8 polyclonal cells. The common clinical features include bilateral enlargement of parotid glands that are often massive, sicca syndrome and lymphocytic interstitial pneumonitis. Additionally, hepatitis, polyarthritis, polymyositis and generalized lymphadenopathy may occur. DILS may improve with ART but the response is often variable and manifestation outside the parotid gland may respond to systemic corticosteroids while enlarged parotid gland may be treated by aspiration of parotid cyst and instillation of a scelerosant for cosmetic reason.

5→GIT related complications

- **Cpsp examiners would expect from you the major complications and their treatment and therefore, we would focus here mainly on treatment only.**

i) oropharyngeal candidiasis

- it is nearly always caused by C.albicans and may present as pseudomembranous candidiasis(white patches on the buccal mucosa) , erythematous candidiasis(presents as a reddened mucosa and smooth shiny tongues)
- It is treated by topical antifungals and antifungal lozenges are more effective than solution .systemic azole therapy like fluconazole is indicated if topical therapy is ineffective or there is esophageal involvement.

ii) esophageal candidiasis

- Patients present with pain on swallowing, dysphagia and regurgitation and there is concomitant oral candidiasis in 70% of cases. it is treated with Fluconazole (100-200mg daily) for 2-3 weeks and if there is no improvement patients should be investigated with oesophagoscopy with biopsy to look for CMV or herpes simplex ulcerations
- herpes simplex infection is treated with acyclovir (400mg TDS) for 5-7 days or 5mg/kg intravenously for severe cases .additionally , famciclovir(500mg BD for 5-10days) may also be used .for acyclovir resistant cases , foscarnet 40mg/kg IV TDS may be used .

iii) HIV cholangiopathy

It is a form of secondary scleroing cholangitis and it is common in patients with severe immune suppression. it is diagnosed by ERCP which shows intraluminal irregularities of proximal intrahepatic ducts with pruning of the terminal duct at the papilla is commonly seen . Papillary stenosis is common and amenable to cautery via ERCP .CMV, cryptosporidium and microspordia are thought to play an inciting role .treatment is ART.

Scanned with CamScanner

iv) Enterocolitis (due to Cryptosporidium)

- Present as profuse watery diarrhea. it is more common in HIV infected patient than uninfected individuals .there is a wide range of agents known to cause Enterocolitis including Bacteria (salmonella , shigella) Viruses (CMV , adenovirus) , and protozoans (Cryptosporidium &Entamoeba histolytica etc.) .
- Due to wide range of causative agents a stool culture and multiple stool examination for ova & parasites including **modified acid-fast staining for cryptosporidium** should be performed.
- patients with negative stool examination and persistent symptoms (and CD4 count less than 100cells/mm^3 should be evaluated with colonoscopy with biopsy (ulcers mostly in left sided colon showing typical owl's –eye inclusion bodies) for CMV colitis

Treatment

- ART and diarrhea can be treated with diphenoxylate with atropine(tab lomotil ®) 2-4 tablets per day .Additionally , Octreotide has been found effective in diarrhea caused by cryptosporidium
- **enteritis** →may be due to one of the three organism namely cryptosporidiosis
- microsporidiosis and cystoisosporiasisi which are intracellular parasites and if stool microscopy is negative at least two times then go for a duodenal biopsy

- About 40 % of patients with disseminated MAC may present with watery diarrhea and prominent fever (it differentiate MAC from above mentioned 3 parasites)

Common causes of chronic water diarrhea in HIV patients

	Cryptosporidiosis	Microsporidiosis	Cystoisosporiasisi (formerly isosporiasis
Organism	Protozoan	Fungus	Protozoan
Species	Cryptosporidium parvum C.hominis	Enterozoon bieneusi encephalitozoon intestinalis etc	Cystoisospora belli
Animal host	Multiple	Multiple	No
Distribution	Global	Global	Tropics
Stool examination	Acid-fast stain	Trichrome stain polymerase chain reaction	Acid- fast stain
Specific treatment	No established therapy	Albendazole (some species)	Co- trimoxazole

(V) Hepatitis (Hepatic disease)

Scanned with CamScanner

- HIV does not cause hepatitis by itself but due to co-infection with HBV &HCV, CMV, hepatotoxicity with antiretroviral therapy and other opportunistic infections due to immune suppression.

A) HIV &HCV co-infection

- Treatment regimen depends on genotype, resistance profile, weather the patient is treatment naïve or not, as well as whether or not the patient has cirrhosis and if so, whether it is compensated or decompensated.
- HIV co-infection increases HCV viremia and ↑ the risk of viremia and risk of liver fibrosis and hepatocellular carcinoma .Treatment for HCV should be preferably be deferred in patients with CD4 counts < 200 cells /mm^3 until they are stable on ART .
- Sofosbuvir & ledipasvir for 3months is the preferred regimen and response to anti-HCV therapy is similar to HIV –uninfected patients. Daclatasvir should be avoided due to interaction

B) HIV & HBV co-infection

- HIV coinfection ↑ HBV viremia, is associated with less elevation of transaminase (possibly due to immune suppression) and increase risk of liver fibrosis and hepatocellular carcinoma .HBV status should be checked at baseline in all HIV –infected patients .A flare of hepatitis may be associated with improved immune function after starting ART or discontinuing antiretroviral that have anti-HBV activity
- HIV & HBV co-infection should be treated with antiretroviral regimens that include medications with activity against both viruses like TDF or TAF, lamivudine or emtricitabine / doltegravir. so the 3 drug should be continue almost lifelong

6→Endocrinology complication

- Hypogonadism is probably the most common endocrine abnormality in HIV –infected men
- in AIDS patient adrenal glands may also be involved (however, prevalence of clinically significant adrenal insufficiency is low)due to infection with CMV , M-Avium complex, infiltration with Kaposi sarcoma , hemorrhage and auto immunity .if symptomatic, such patients may be treated with fludrocortisone(0.1-0.2 mg)

7→Mucocutaneous Disease

i) seborrhoeic Dermatitis

- Severity correlates with falling CD4 counts. it responds well to a combined topical antifungal and glucocorticoid .Selenium sulphide shampoo is also helpful

ii) Herpes simplex infection

Scanned with CamScanner

- It is very common and affects primarily the nasolabial and anogenital. Ulcers that persist for more than 4 weeks are AIDS-defining. Diagnosis is clinical but PCR of vesicles fluid or from ulcer swabs may be diagnostic with unusual presentation
- it should be treated with acyclovir (400mg orally TDS) for 5-10 days or Famciclovir (500mg BD) or Valcyclovir(500mg BD) .response is good but relapses are common .frequent relapses that persist despite ART should be treated with long-term herpes prophylaxis with acyclovir (400mg BD for 6-12 months)

iii) Herpes Zoster

- the median CD4 counts at first episode of zoster is 350 cells/mm^3 .the rash may be multidermatomal in advance disease
- patient with herpes zoster should be treated with famciclovir(500mg TDS) or Valacyclovir(500mg TDS) or acyclovir (800mg 4-5 times /day) for 7-10 days
- Disseminated zoster and patients with ocular involvement should be treated with intravenous acyclovir 10mg/kg TDS for 7-10 days.
- the recombinant zoster vaccine (Shingrix®) two doses administered 2-6 months apart , can be given to HIV-infected patients (as it is not –live vaccine contrary to previous vaccine named Zostavax).

iv) Molluscum Contagiosum

- it is caused by a pox virus and should be treated with topical liquid nitrogen

v) Nail Disorders

- Fungal infections (onychomycosis) are very common and often involve multiple nails .Blue-black discoloration of nails is a common finding and may be due to HIV or to the antiretroviral drug zidovudine

vi) Bacillary angiomatosis

- It is caused by bacteria named Bartonella henselae or B. quintana. Skin lesion range from solitary superficial red-purple to multiple subcutaneous nodules or plaques .the infection may become disseminated with fever, lymphadenopathy and hepatosplenomegaly. Diagnosis is made by biopsy of a lesion and Warthin- Starry silver staining. This reveals aggregates of bacilli. Treatment with doxycycline or azithromycin is effective.

vii) Vaginal candidiasis

- It can be treated with a single dose of antifungal agent like fluconazole (150mg) .resistant or recurrent infection should be treated with fluconazole (100-200) for at least 7 days.

Scanned with CamScanner

8→ Common Cancer in HIV infected patients

Approximate incidence ratio of virus –related cancers compared to the general population	
Viral cancers	**Incidence ratio**
Human herpes virus 8- related	3600
Kaposi's sarcoma	
Epstein- bar virus-related	80
Non Hodgkin lymphoma	10
Hodgkin lymphoma	
Human papillomavirus –related	6
Cervical cancer	6
Vulvar cancer	30
Penile cancer	4
Hepatitis B/C virus related	
Hepatocellular	5

i) **Kaposi sarcoma**

- It may be confused with other vascular lesions such as angiomas and pyogenic granuloma. Patients with mild to moderate forms of Kaposi sarcoma do not require .any specific treatment as it resolves with effective ART and sometime lesion may be flare when ART is first started. Advance disease is effectively treated with combination chemotherapy **like DBV** (daunorubicin, bleomycin, and vinblastine) and Pomalidomide 5mg/day on days 1-21 of every 28-days cycle.

ii) **Non-Hodgkin lymphoma**

- Most commonly diffuse large B –cell tumor and more than 70% cases are extra nodal. Prognosis depends upon degree of immunodeficiency at the time of diagnosis.
- Treatment is ART and radiation for CNS lymphoma that is effective while systemic disease is treated with combination chemotherapy **like EPOCH** (etoposide, prednisolone, vincristine, cyclophosphamide and doxorubicin) and filgrastin (G-CSF) is used to maintain white blood counts.

iii) **Invasive cervical cancer**

- Vaginal candidiasis, cervical dysplasia, neoplasia and pelvic inflammatory disease are more common in HIV-infected woman than uninfected and that is why HIV infected women needs frequent surveillance and care.
- **screening for cervical cancer**

Scanned with CamScanner

A) women aged < 30 years

- for women younger than 30-year , a Papanicolaou smear (pap smear) should be performed within a year of the onset of sexual activity and then yearly .after 3 consecutive negative examination ,screening should be done every 3 years .HPV DNA testing of cervical specimen is not recommended in this age women

B) women ≥ 30 years

- for women ≥ 30 years , screening should be continue even beyond age 65 contrary to general population . There are two screening protocol for this group, cytology alone and cytology with HPV DNA cotesting.
- Pap smear is done when HIV is diagnosed and then yearly .However, after 3 negative smears, it should be done every 3 yearly. Alternatively Pap smear with cotesting for HPV DNA can be performed when HIV is diagnosed or starting when patients are age≥ 30-year .IF Pap smear is normal and HPV test is negative , then the next screening should be done every 3 yearly
- the management of abnormal PAP smear and positive HPV tests is same in HIV infected and uninfected women

9→ HIV-associated Renal Disease

- acute renal injury is a common entity in HIV infected patient possibly due to acute infection or as result of drugs like tenofovir and amphotericin
- HIV-associated nephropathy (HIVAN) is the leading cause of CKD in HIV-infected patients and progress rapidly to end-stage disease .HIVAN present with CKD or nephrotic syndrome or both
- ART has some effect is slowing down the process

10 → Cardiac Disease

- HIV-associated cardiomyopathy may be confused with idiopathic dilated cardiomyopathy
- there is increased risk of myocardial infarction due to accelerated atherogenesis caused by inflammatory state and dyslipidemia(caused by some antiretroviral drugs)

11→Syphilis in HIV infected patients

- due to ↑ risk of syphilis in HIV infected individuals (esp. among MSM) , and increased risk of reactivation of syphilis and progression to tertiary syphilis despite proper treatment , all such patients should undergo screening for syphilis by a rapid Plasma reagin(RPR) or Venereal Disease Research Laboratories (VDRL) every 6 monthly and if positive it should be treated
- Due to serological nature of screening tests and disordered antibody production in HIV-infected patients , therefore , a non-reactive treponemal test does not exclude infection
- if there is reactive RPR, VDR test of ≥ 1 year durations , all such patient should have a lumbar puncture **for CSF R/E & VDRL test** and if the test is **normal**[1] then patient should be treated **for latent syphilis** with benzathine penicillin G (2.4 million units intramuscularly weekly for 3 weeks) with follow-up titers and those with **pleocytosis or positive VDRL** should be treated for neurosyphilis with aqueous penicillin G(2.4 million units intravenously every 4 hours and probenecid for 10 days or procaine penicillin G(2.4 million units IM daily with probenecid

Scanned with CamScanner

500mg four times daily for 10 days) followed by weekly benzathine penicillin G 2.4 million units intramuscularly for 3 weeks.

- there were HIV-infected cases with secondary syphilis having negative serological testing for syphilis.

12→Immune Reconstitution Inflammatory Syndromes (IRIS)

- IRIS is a common early complication of ART , especially in patients who start ART withCD4 counts below 50 cells /mm^3
- it is the diagnosis of exclusion and the diagnosis of IRIS can be made confidently only after recurrence or new opportunistic infection has been ruled out as cause of clinical deterioration
- it is of two types type I is characterized by unmasking of a new infection while type II is manifested by paradoxical deterioration of an existing opportunistic disease including infection that responding to appropriate therapy
- The clinical presentation of IRIS events is often characterized by an **exaggerated immune response**, with pronounced inflammatory features like vitritis has developed in patients with CMV retinitis after they have been treated with antiretroviral treatment.
- Management of IRIS is **conservative and supportive** with the use of corticosteroids only for severe reactions and ART should not be stopped unless the IRIS reaction is life – threatening.

Chemoprophylaxis for complications of HIV infection

1) **Prophylaxis against pneumocystis pneumonia**

- when HIV infected patient have CD4 counts below 200 cells/mcL or CD4lymphocytes percentage below 14% , or weight loss or there is oral candidiasis , they should be offered **primary prophylaxis** for pneumocystis pneumonia
- patients with a history of pneumocystis pneumonia should be offered **secondary prophylaxis** until their viral load is undetectable and they have maintained a CD4 counts of ≥200 cells/mcL for more than 3 months while on ART
- Trimethoprim-sulfamethoxazole double strength (tab Septran DS) OD or 3 times/week .other options include Dapson and Atovaquone.

2) **Prophylaxis against M avium M avium complex infection**

- HIV –infected patients whose CD4 counts fall to below 75-100 cells/mcL should be given prophylaxis against M avium complex infection. regimen is Clarithromycin 500mg BD daily and or Azithromycin 1200mg/weekly ↓ the incidence of disseminated M avium complex infection by 75%.it should be continue until CD4 rises above 100 cells/mcL for more than 3 -6 months while on ART

3) **Prophylaxis against toxoplasmosis**

- it is indicated in HIV –infected individual having CD4 cell counts below 100 cells/mcL and or positive IgG toxoplasma serology .protection is provided with Trimethoprim-sulfamethoxazole double strength (tab Septran DS) daily OD or combination of

Scanned with CamScanner

pyrimethamine 25mg once a week plus leucovorin 25mg weekly and Dapson 50mg daily. it should be continue until CD4 counts have increased > 200 cells/mcL for more than 3 months.

4) Prophylaxis against Cryptococcosis

- when CD4 counts fall below 100 cells /mcL , serum cryptococcal antigen test should be advised and if it is positive ,prophylactic therapy with fluconazole should be initiated

5) Tuberculosis secondary prevention

- HIV –infected individual are more prone to tuberculosis and therefore they should undergo investigation like **PPD** and **IGRA blood test** at baseline and then yearly if still exposed to risk of tuberculosis. those with positive PPD **(>5mm induration)** or IGRA blood test should further be investigated for active tuberculosis including by a chest x-ray and if features (infiltrate at any location, mediastinal adenoapthy) are suggestive, they should have sputum for acid fast bacilli and if positive then they should be treated for active tuberculosis as outlined before .while patient with positive PPD or IGRA assay having normal chest-xary and negative sputum is labeled as **latent tuberculosis** .in patient with advanced disease may have false negative tests and it may be worth retesting once CD4 become≥200 cells/mcL . patient with latent TB who have not been previously treated for (active or latent) TB should be treated with isoniazid (900mg) and rifapentine (900mg) weekly (patient having weight 50 kg) for 12 weeks and another regimen is rifampicin 600mg daily for 4 months and isoniazid 300mg for 9 months .

Immunization in HIV patients

- immune response to vaccination are impaired in HIV-infected individuals and therefore if CD4 counts is below 200 cells/mcL, then immune response to immunization are very poor and therefore it is preferable to wait until CD4 count has increased to more than 200cells/mcL while on ART. HIV –infected individuals should receive the standard inactivated vaccines while most of the live vaccine (except measles vaccine) should be avoided as this may result in disease from the attenuated organism. Additionally, if HIV-infected patients having negative HBV surface antigen/antibody, they should be vaccinated against HBV and if patient does not have the immunity 1 month after the 3-shots series, then the series should be repeated.

Scanned with CamScanner

HIV Prevention

Prevention measures for HIV transmission
Sexual
• Sex education programs in school • Easily accessible voluntary counselling and testing centres • Promotion of safer sex practices (Delaying sexual debut, condom use, fewer sexual partners) • Effective ART for HIV-infected individuals • Pre-exposure prophylaxis for high-risk groups • Male circumcision • Post-exposure prophylaxis
Parenteral
• Blood product transmission: donor questionnaire, routine screening of donated blood • Injection drugs use: education, needle/syringe exchange, avoidance of "shooting galleries, methadone maintenance programs.
Perinatal
• Routine `opt out` antenatal HIV antibody testing • Measures to reduce vertical transmission (see text)
Occupational
• Education/training: universal precautions , needlestick injury avoidance • Post-exposure prophylaxis

Primary Prevention

- safe sexual practice , HIV testing & screening and ART

Preexposure antiretroviral treatment prophylaxis (PrEP)

- sexually active men who have sex with men , male to female transgender persons , and heterosexuals and bisexual women who are likely to have partners with HIV risks and injection drug user should definitely be considered for PrEP . After taking PrEP, HIV antibody & pregnancy test should be carried out after every 3 months and serum creatinine every 6 months.

PrEP prescription

- Emtricitabine /TDF (Truvada®) one tablet daily for 30-90 days and then for 90 days while double dose is recommended on day 1 for men who have sex with men
- Emtricitabine /TAF (Descovy®) one tablet daily for 30-90 days and then for 90 days, However, it is not tested in women.
- the above mentioned regimen can reduce the risk of sexual transmission of HIV among uninfected individuals at high risk for infection while alterative effective option is latex or polyurethane condoms .However , if individual have a known HIV-infected partner ,he may want the extra protection of PrEP

Post exposure prophylaxis (PEP) for HIV

- the aim is to reduce or prevent local viral replication prior to dissemination such that the infection can be aborted

Scanned with CamScanner

- Treatment should be started sooner and within 72 hours of exposure to HIV after a careful assessment in both occupational and non-occupational settings while treatment is not recommended after more than 72 hours after exposure.
- The preferred regimen is **TER** e.g. tenofovir (300mg) emtricitabine (200mg) daily and raltegravir (400mg) twice a day for 1 month and but PEP should not be given if the exposed person is HIV-infected.

- HIV antibody testing should be performed at 3 months after exposure and if positive then patient should be properly treated (see below)

Prevention of perinatal transmission of HIV

- All pregnant women should be screened and if positive should be treated irrespective of viral load. The recommended regimens are zidovudine and lamivudine with either ritonavir-boosted lopinavir or ritonavir-boosted atazanavir. C-section should be done if HIV viral load is greater than 1000 copies/mL near the delivery. zidovudine should be offered to infant after birth for 6 weeks and breastfeeding should be avoided

Prevention of HIV Transmission in Health Care Settings

- the risk of HIV transmission from a needle stick with blood from an HIV –infected patient is about 1: 300 and risk is higher with deep punctures , large inoculum and source contain high viral load
- Health professional who sustain needle sticks injury should be counseled and tested for HIV infection and if negative then follow-up testing performed at 6 weeks, 3months and 6 months.
- the preferred regimen is TDF300mg with emtricitabine 200mg (Truvada) daily along with raltegravir 400mg BD for 4 weeks as described earlier

Prevention of HIV Transmission through blood or blood products

Screening of blood and blood products have lowered the risk of HIV transmission via this route .When blood transfusion from an HIV-infected donor occours, the risk of transmission of HIV is 95%

Prevention of HIV via Vaccination (Recent advances)

- **RECOMBINANT CANARYPOX** with two booster doses
- It is primarily for heterosexual population and its efficacy is low for widespread use (31%)

Surgeon infected with HIV

- If affected surgeon viral load is less than 200 he can perform invasive procedures and if viral load is more than 1000 he is not allowed to do surgeries.

Treatment of HIV

As we have discussed treatment of opportunistic infection, malignancies, complications of HIV infections and prophylaxis for opportunistic infection, now we will discuss briefly treatment of HIV infection itself as detail discussion is beyond the scope of this book.

Scanned with CamScanner

- Guidelines now recommend starting ART in all people with confirmed HIV infection, irrespective of CD4 counts or clinical status after proper and detail discussion. in patient with major opportunistic infections, ART should be started within 2 weeks with two exception and that is cryptococcal meningitis where ART should be deferred for 5 weeks as early ART may ↑ the risk of mortality and another exception is tuberculosis where ART should be delayed 8 weeks (except if CD4 counts are below 50 cells/mcL) after initiation of ATT due to increased risk of immune reconstitution syndrome.
- antiretroviral medications can be grouped into six major groups
  - (i)nucleoside & nucleotide reverse transcriptase inhibitors NRTIs
  - (ii)non-nucleoside reverse transcriptase inhibitors NNRTIs
  - (iii) protease inhibitors
  - (iv) Integraase inhibitors
  - (v) entery and fusion inhibitors
  - (vi) attachment inhibitors

For detail discussion of each class, reader is advised to see a reference book like CMDT

- If treatment is started before the result of resistance testing are available, NNRTI should not be used in treatment naïve patients

Constructing an initial regimen for HIV treatment

Key points

- Primary goal of therapy should be complete suppression of viral replication as measured by the serum viral load.
- AIDS developed within 10 years in almost 50% of untreated seropositive individuals.
- regimens with the strongest evidence contain Integraase inhibitors like dolutegravir (associated with neural tube defect in children's of women taking it during pregnancy) and bictegravir
- The safest, most effective and easiest to use nucleoside & nucleotide reverse transcriptase inhibitors (NRTIs) are TDF and TAF followed by emtricitabine or lamivudine .However, TAF is preferred in patients with renal dysfunction, osteoporosis or osteopenia.
- Although the HIV treatment protocol has been for three drugs from atleast two different classes ,however , **there are Recent Advances** where two drugs regimen has developed like combination of dolutegravir and lamivudine (Dovato®).However , it is not recommended for patients with high viral load (> 500,000) ,co-infection with HBV (resistance development by HBV)and patient in whom HIV resistance testing is not available .other two drugs regimen are dolutegravir and rilpivirine(Juluca®) which is indicated for patients who have been successfully virally suppressed for at least 6months ,no HX of treatment failure and not resistant two drug regimen and Cabotegravir with rilpivirine as **a once –monthly intramuscular** injection .

Drug resistant HIV

Scanned with CamScanner

- if HIV is resistant to first line regimens ,then the 2nd line regimen should be consist of three medications from at least two different classes to which the virus is not resistant
- **Recent advances** FDA has approved **Fostemsavir** (an attachment inhibitor) and more recently **Ibalizumab** (a monoclonal antibody) specifically for multidrug-resistant HIV **(MDR-HIV)** who is not responding to their existing regimen and they are used in combination with others antiretroviral drugs.

Treatment of HIV during pregnancy

- It is recommended that all pregnant women should have HIV testing .it is noteworthy that CD4 counts falls by 25% during pregnancy due to hemodilution and the natural course of HIV is not altered by pregnancy. In pre-ART era, the rate of mother-child transmission was 15-40% and now it has dramatically reduced to less than 1%. C-section is associated with lower risk of transmission than vaginal delivery, however, if the viral load is suppressed then, mode of the delivery does not affect transmission risk .generally vaginal delivery is indicated if the viral load is less than 1000 copies /ml and C-section is preferred when it is > 1000 copies/ml. as HIV is transmitted by breastfeeding , exclusive formula feeding is recommended in high-income individuals and however , due to ↑ infant morbidity and mortality associated with formula feeding in resource poor countries , infant should be breastfeed(particularly in mothers with suppressed viral load) .
- Recommended drugs in pregnancy include atazanavir /ritonavir, darunavir/ritonavir, efavirinze and rilpivirine .dolutegravir is associated with neural tube defects.
- The treatment regimens during pregnancy are zidovudine, lamivudine and ritonavir boosted lopinavir or zidovudine, emtricitabine and nevirapine.
- after birth of infant to HIV positive mothers, they should be started on syp zidovudine for 6 months and diagnosis of HIV in infancy require the detection of HIV RNA by PCR, as maternal antibodies to HIV, persists for up to 15 months, **will give a false-positive result on antibody assays.** PCR should ideally be carried out within 6 weeks of birth to facilitate early ART initiation. If the baby is breastfed, the PCR should be repeated 2 weeks after weaning.

Monitoring antiretroviral treatment (efficacy and toxicity)

- Patients who are intolerant of initial regimen should be switched to an alternative regimen .CD4 counts and HIV viral load should be repeated 1-2 months after starting treatment or change of the regimen and then every 3-6 months thereafter in clinical stable patients. While with Integrase included regimen majority of patients will have undetectable HIV viral load at 1 month. all patients should have undetectable viral load by 3 months and if it is not ,it is mostly due to noncompliance and therefore adherence support should be enhanced if virological failure is detected and measurement of the viral load repeated to confirm failure before switching to a new ART regimen.CD4 counts increases rapidly in the first month ,followed by a more gradual increases .in the first year , CD4 counts typically increases by 100-150 cells/mm^3 and about cells/mm^3 per annum thereafter until the reference range is reached ,provided the viral load is suppressed. in minority of patients the CD4 counts does not

Scanned with CamScanner

increases despite virological suppression and similarly in certain patient CD4 response is optimal despite the presence of virological failure

Available Brands

i) **Descovy200mg/25mg→** containing Emtricitabine and tenofovir alafenamide TAF

ii) **Truvada 300mg/200mg→**contaning tenofovir disoproxil fumarate (TDF) and emtricitabine

⇒Pakistani regimens

(1) Tab Viropil ⇒TLD regimen (containing tenofovir disoproxil fumarate 300mg, Lamivudine 300mg and Dolutegravir)

TLE regimen ⇒(2) Tenofovir disoproxil fumarate, Lamivudine and Efavirinze

Adverse effects of ART

1) NRTI

- **zidovudine** is most commonly associated with lipoatrophy while didanosine is the 2nd most common culprit .zidovudine also causes anemia and neutropenia and it is treated by erythropoietin (if it is less than 500milli units /mL) 8000units subcutaneously and filgrastin(G-CSF) respectively .
- **lamivudine & emtricitabine** dose should be ↓ in CKD patients
- **Abacavir** is associated with ↑ risk of MI and should be voided in high risk cardiovascular patients
- **Tenofovir** (TDF&TAF) .TDF is associated with clinically modest loss of kidney function and ↑ rate of bone resorption while TAF is associated with fewer problems and is the preferred choice.
- **Didanosine** is associated with pancreatitis and dose-dependent peripheral neuropathy. it is also associated with fulminant hepatic failure and hypocalcaemia and hypomagnesaemia and that is why it is rarely use these days

2) NNRTIS

- **Efavirinze** is associated with rash and psychiatric / neurological adverse symptoms like delusion , mania and strange dreams
- **Nevirapine** is most commonly associated with rash and sometime with hepatotoxicity

3) Protease inhibitors (PIs)

- medication interaction are common and each can inhibit and induce various liver enzymes and all PIs except atazanavir are associated with lipid disorder ,insulin resistance, diabetes mellitus ,abdominal obesity and buffalo hump (metabolic syndrome) . It is also associated with liopodystrophy (lipid abnormalities and change in body habitus) and cardiac conduction e.g. prolong PR interval.
- **Indinavir⇒** is associated with UTI, indinavir induced AKI and indirect hyperbilirubenemia.
- **Atazanavir** is most commonly associated with mild hyperbilirubenemia; nephrolithiasis and cholelithiasis .proton pump inhibitors are contraindicated with this drug as it require an acidic PH to remain in solutions.

4) Integrase inhibitor

- **Raltegravir** is associated diarrhea, nauseas and headache.

Scanned with CamScanner

- **Dolutegravir** inhibit tubular secretion of creatinine and therefore associated with small increase in serum creatinine and neural tube defects in offspring of mother who took it at conception.

5) Entry and fusion inhibitors

- **Maraviroc** (CCR5 co-receptors antagonist) is associated with cough, fever, rash, abdominal pain and musculoskeletal problems.
- **Ibalizumab** is associated with diarrhoea, ↑ creatinine and lymphopenia.

6) Attachment inhibitor

- **Fostemsavir** should not be used concomitantly with enzyme inducer medications

Knowing this much about HIV is enough to pass your long case viva

Scanned with CamScanner

PANCREATIC PATHOLOGIES IN MEDICINE

Written by Dr Sayyad Ahmed
(EX-PGR Gastro ATH)

Acute Pancreatitis

Definition of Acute Pancreatitis

Acute pancreatitis is confirmed if at least two of the following conditions are present:

1. Typical Abdominal Pain: Pain consistent with the clinical presentation of acute pancreatitis.
2. Elevated Enzymes: Amylase and/or lipase levels elevated to at least three times the upper limit of normal.
3. Diagnostic Imaging: Imaging studies showing characteristic features of acute pancreatitis

Etiology of Acute Pancreatitis

The most common causes of acute pancreatitis include gallstones and excessive alcohol consumption. Additionally, other potential causes are:

- Post-ERCP Pancreatitis: Inflammation of the pancreas following an endoscopic retrograde cholangiopancreatography (ERCP) procedure
- Metabolic Disorders: conditions such as hypertriglyceridemia (high levels of triglycerides) and hypercalcemia (high levels of calcium)
- Traumatic Injury: Physical injury to the abdominal area
- Genetic Factors: Certain genetic mutations can predispose individuals to recurrent episodes of acute pancreatitis and can progress to chronic pancreatitis.
- Drug-Induced Pancreatitis: Various medications can trigger pancreatitis, including azathioprine, 6-mercaptopurine, valproate, ACE inhibitors, aminosalicylates, and furosemide.
- Anatomic Abnormalities: Structural abnormalities of the pancreaticobiliary system, such as an anomalous pancreaticobiliary junction, biliary cysts, annular pancreas, and pancreas divisum, can lead to pancreatitis

Classification of Acute Pancreatitis

Based on Severity:

- Mild Acute Pancreatitis: No organ failure. No local or systemic complications. Usually resolves within the first week.
- Moderately Severe Acute Pancreatitis: Transient organ failure (resolves within 48 hours). Local or systemic complications without persistent organ failure.
- Severe Acute Pancreatitis: Persistent organ failure (one or more organs) lasting more than 48 hours. May include systemic complications such as respiratory failure, renal failure, or shock

Scanned with CamScanner

Based on Etiology:

- Gallstone Pancreatitis: Caused by gallstones obstructing the bile duct.
- Alcohol-Induced Pancreatitis: Associated with chronic heavy alcohol use.
- Hyperlipidemic Pancreatitis: Due to high levels of lipids in the blood.
- Drug-Induced Pancreatitis: Caused by certain medications.
- Traumatic Pancreatitis: Resulting from physical injury to the pancreas.
- Post-ERCP Pancreatitis: Following an endoscopic retrograde cholangiopancreatography procedure.
- Infectious Pancreatitis: Caused by infections such as mumps or hepatitis.
- Idiopathic Pancreatitis: When no specific cause is identified.

Based on Morphological Criteria:

- Interstitial Edematous Pancreatitis: Characterized by pancreatic enlargement due to inflammatory edema. No necrosis.
- Necrotizing Pancreatitis: Presence of pancreatic and/or peripancreatic necrosis. Can be sterile (without infection) or infected

Based on Complications:

- Local Complications: Acute peripancreatic fluid collection. Pancreatic pseudocyst. Acute necrotic collection. Walled-off necrosis.
- Systemic Complications: Exacerbation of pre-existing comorbidities (e.g., cardiac, pulmonary, renal conditions). Systemic inflammatory response syndrome (SIRS) (Banks et al., 2013).

Prognostic Scores

- Ranson's Criteria: Based on clinical and laboratory findings within the first 48 hours
- APACHE II (Acute Physiology and Chronic Health Evaluation): Based on initial severity of illness
- BISAP (Bedside Index of Severity in Acute Pancreatitis): Based on five parameters including blood urea nitrogen, impaired mental status, SIRS, age, and pleural effusion
- CT Severity Index (CTSI): Based on findings from a contrast-enhanced CT scan

Imaging of Acute Pancreatitis

Acute pancreatitis is an inflammatory condition of the pancreas that can range from mild to severe. Imaging plays a crucial role in the diagnosis, assessment of severity, and management of acute pancreatitis. The primary imaging modalities used are:

1. Ultrasound (US)
2. Computed Tomography (CT)
3. Magnetic Resonance Imaging (MRI)
4. Endoscopic Ultrasound (EUS)
5. Magnetic Resonance Cholangiopancreatography (MRCP)

1. Ultrasound (US)

Scanned with CamScanner

- First-line Imaging Modality: Often the initial imaging study performed due to its availability and lack of radiation.
- Uses: Identifying gallstones, biliary dilatation, and assessing pancreatic size and echotexture.
- Limitations: Limited by bowel gas and patient body habitus (Singh et al., 2019).

2. Computed Tomography (CT)

- Gold Standard for Acute Pancreatitis: Provides detailed images of the pancreas and surrounding structures.
- Uses:
  - Confirming the diagnosis.
  - Assessing the severity of pancreatitis.
  - Detecting complications such as necrosis, abscesses, pseudocysts, and vascular complications.
- CT Severity Index (CTSI): Used to assess the severity and prognosis based on pancreatic inflammation and necrosis

3. Magnetic Resonance Imaging (MRI)

- Alternative to CT: Particularly useful for patients with contraindications to CT or when detailed ductal anatomy is required.
- Uses:
  - Evaluating pancreatic ductal system.
  - Differentiating between fluid collections and solid components.
  - Detecting biliary obstructions and pancreatic necrosis.
- Advantages: No radiation exposure and superior soft-tissue contrast (Singh et al., 2019).

4. Endoscopic Ultrasound (EUS)

- High-Resolution Imaging: Provides detailed images of the pancreas and biliary tree.
- Uses:
  - Detecting small gallstones or sludge not seen on transabdominal US.
  - Assessing for pancreatic masses or neoplasms.
  - Performing fine-needle aspiration (FNA) for diagnostic purposes (Singh et al., 2019).

5. Magnetic Resonance Cholangiopancreatography (MRCP)

- Non-Invasive: Provides a detailed view of the pancreatic and biliary ducts without the need for contrast agents.
- Uses:
  - Detecting biliary and pancreatic ductal abnormalities.
  - Evaluating the cause of pancreatitis, such as choledocholithiasis or strictures.
- Advantages: Non-invasive and excellent ductal imaging without radiation

Scanned with CamScanner

Assessing the Severity of Acute Pancreatitis

Assessing the severity of acute pancreatitis is crucial for determining the appropriate level of care and guiding management decisions. The severity of acute pancreatitis can be classified into three categories: mild, moderately severe, and severe. Various clinical, laboratory, and imaging criteria are used to assess the severity.

Clinical Assessment

1. Initial Presentation
    - Symptoms: Severe abdominal pain, nausea, vomiting, fever.
    - Physical Examination: Abdominal tenderness, guarding, and possible signs of systemic inflammation (e.g., tachycardia, hypotension)
2. Systemic Signs
    - Signs of systemic inflammatory response syndrome (SIRS): fever or hypothermia, tachycardia, tachypnea, and leukocytosis or leukopenia.
    - Organ failure: respiratory failure, renal failure, shock

Laboratory Assessment

1. Pancreatic Enzymes
    - Serum Amylase and Lipase: Elevated levels (more than three times the upper limit of normal), although the degree of elevation does not correlate with severity (Banks et al., 2013).
2. Inflammatory Markers
    - C-Reactive Protein (CRP): Levels above 150 mg/L within the first 48 hours can indicate severe pancreatitis (Singh et al., 2019).
    - Procalcitonin: Elevated levels may suggest severe inflammation and infection
3. Other Laboratory Tests
    - Blood Urea Nitrogen (BUN): Elevated levels can indicate dehydration and correlate with severity
    - Hematocrit: An increase can suggest hemoconcentration and severity.
    - Creatinine: Elevated levels may indicate renal impairment

Scoring Systems

1. Ranson Criteria: Assesses severity based on initial and 48-hour clinical and laboratory findings.
    - On Admission: Age > 55 years, WBC > 16,000/mm³, glucose > 200 mg/dL, AST > 250 IU/L, LDH > 350 IU/L.
    - At 48 Hours: Hematocrit decrease > 10%, BUN increase > 5 mg/dL, calcium < 8 mg/dL, PaO_2 < 60 mm Hg, base deficit > 4 mEq/L, fluid sequestration > 6 L
2. APACHE II (Acute Physiology and Chronic Health Evaluation II): Used for critically ill patients, assessing severity based on a range of physiological variables within the first 24 hours of ICU admission
3. BISAP Score (Bedside Index for Severity in Acute Pancreatitis): Simple bedside scoring system using five criteria: BUN > 25 mg/dL, impaired mental status, SIRS, age > 60 years, and pleural effusion

Scanned with CamScanner

4. CT Severity Index (CTSI): Based on findings from contrast-enhanced CT, assessing the extent of pancreatic inflammation and necrosis

Supportive Care

IV Fluids:

- Administer an initial bolus of 1-2 liters of intravenous fluids (IVF), followed by maintenance IVF at a rate of 250-500 ml per hour.
- Inadequate resuscitation can lead to decreased pancreatic perfusion, increasing the risk of necrotizing pancreatitis and end-organ failure, such as renal failure from acute tubular necrosis.
- Goal-directed IVF therapy is recommended by the American Gastroenterological Association (AGA) to maintain target mean arterial pressure, central venous pressure, blood urea nitrogen (BUN), and hematocrit levels.
- Signs of inadequate resuscitation include increasing hematocrit levels, tachycardia, hypotension, and decreased urine output

Nutrition

Early Oral Feeding:

- Early oral feeding within 24 hours is recommended. Routine nil per oral (NPO) orders are not necessary

Enteral Feeding:

- If patients with acute pancreatitis are unable to tolerate oral intake within 72 hours, enteral feeding via a nasogastric or nasojejunal tube is the preferred method.
- Enteral feeding is associated with fewer complications compared to parenteral nutrition
- Limitations to enteral feeding include severe ileus and difficulty inserting a nasojejunal tube.
- Randomized trials have shown that in severe acute pancreatitis, nasogastric tube feeding is as safe and effective as nasojejunal feeding. Therefore, nasogastric feeding is an acceptable alternative if a nasojejunal tube cannot be placed

Subsequent Abdominal Imaging

CT Scan:

- An abdominal CT scan with contrast to assess for pancreatic necrosis is indicated in patients with severe acute pancreatitis, worsening abdominal pain, or organ failure within 72 hours of admission

Antibiotics

Usage Guidelines:

- Prophylactic antibiotics are not recommended for patients with acute pancreatitis, regardless of the presence of necrosis
- If a patient exhibits signs of systemic inflammatory response syndrome (SIRS) such as tachycardia, leukocytosis, or fever, it is reasonable to start empiric antibiotics while awaiting blood culture results.
- Recommended antibiotics include imipenem-cilastatin, meropenem, or a combination of a quinolone and metronidazole. If cultures are negative and no infection source is identified, antibiotics should be discontinued.

Scanned with CamScanner

ERCP in Acute Pancreatitis

Procedure Goals:

- The goal of Endoscopic Retrograde Cholangiopancreatography (ERCP) is to perform sphincterotomy with stone extraction.

Indications:

- Emergent ERCP (within 24 hours) is indicated for cases of cholangitis.
- Early ERCP (within 24-72 hours) is indicated for patients with severe acute pancreatitis with elevated bilirubin and biliary obstruction.
- Elective ERCP is performed for suspected retained common bile duct (CBD) stones in stable patients.
- A rising bilirubin level or liver enzymes with persistent CBD dilation are strong predictors of choledocholithiasis, warranting an ERCP.
- For cases with a lower suspicion of choledocholithiasis, non-invasive tests such as Endoscopic Ultrasound (EUS) or Magnetic Resonance Cholangiopancreatography (MRCP) can be performed for further evaluation

Cholecystectomy

Indications and Timing:

- Cholecystectomy is recommended for all patients with acute biliary pancreatitis to prevent recurrence.
- Performing the cholecystectomy during the same hospital admission is preferred rather than after discharge.
- In patients with necrosis or fluid collections, defer cholecystectomy until the pancreatitis subsides and these complications stabilize.
- ERCP and sphincterotomy are associated with lower rates of recurrent biliary pancreatitis in patients who do not undergo cholecystectomy

Peripancreatic Fluid Collections in Acute Pancreatitis

Peripancreatic fluid collections in acute pancreatitis are classified based on the timing of their development in relation to the acute pancreatitis episode. These fluid collections may arise following either acute interstitial or acute necrotic pancreatitis and can be either sterile or infected.

Classification:

1. Acute Peripancreatic Fluid Collections (APFC):
    - Develops early in the course of acute pancreatitis, typically within the first 4 weeks.
    - Arises following acute interstitial pancreatitis.
    - Homogeneous, without a defined wall, and contains fluid without necrotic debris (Banks et al., 2013).

Scanned with CamScanner

2. Pancreatic Pseudocysts:
    - Develops from an APFC that persists beyond 4 weeks.
    - Contains a well-defined inflammatory wall and fluid without solid components (Banks et al., 2013).
3. Acute Necrotic Collections (ANC):
    - Develops within the first 4 weeks of acute necrotizing pancreatitis.
    - Contains both fluid and necrotic debris without a defined wall (Banks et al., 2013).
4. Walled-off Necrosis (WON):
    - Develops from an ANC that persists beyond 4 weeks.
    - Contains a well-defined wall and both fluid and necrotic material (Banks et al., 2013).

Management:

- Spontaneous Resolution:
    - Most acute peripancreatic fluid collections resolve on their own.
    - Observation and repeat imaging in 8-12 weeks is a reasonable approach for most patients without signs of infection
- Infected Collections:
    - Infected collections require more urgent intervention, which may include endoscopic, percutaneous, or surgical drainage

Table 1: Updated Atlanta Classification for Peripancreatic Fluid Collections in Acute Pancreatitis

< 4 weeks after acute pancreatitis	> 4 weeks after acute pancreatitis
Acute peripancreatic fluid collection • Contains only fluid, with no defined wall structure • Found around the pancreas • Associated with mild, interstitial edematous pancreatitis, which does not involve tissue death around the pancreas	Pancreatic pseudocyst • Fluid-filled, well-defined cyst without solid components or calcifications • Located around the pancreas • Develops after interstitial edematous pancreatitis *Can also form in chronic pancreatitis
Acute necrotic collection • Contains a mix of fluid and dead tissue without a clear boundary • Located in and around the pancreas • Occurs with severe pancreatitis that involves tissue necrosis	Walled-off pancreatic necrosis • Contains both liquid and solid dead tissue with a well-defined inflammatory wall • Found in and around the pancreas • Develops following severe pancreatitis with tissue death

Scanned with CamScanner

Pancreatic Necrosis Management

Early Enteral Feeding

- Initiate enteral feeding early in the course of pancreatic necrosis to reduce the risk of infected necrosis

Sterile Necrosis Management

- Most patients with sterile necrosis improve with supportive care alone
- Surgical or endoscopic debridement is indicated if there are persistent symptoms such as nausea, vomiting, abdominal pain, or inability to tolerate an oral diet

Prophylactic Antibiotics

- The routine use of prophylactic antibiotics to prevent infected necrosis is not recommended

Infected Necrosis Management

- Patients with infected necrosis require drainage and/or debridement
- In clinically stable patients, supportive care with intravenous antibiotics for at least four weeks is recommended before attempting definitive management. This period allows the necrotic collection to mature, liquefy, and become walled off, facilitating easier debridement
- Routine use of antifungal agents is not recommended

Debridement and Drainage Options

- Minimally Invasive Surgical Approach: This includes laparoscopic drainage and necrosectomy, video-assisted retroperitoneal debridement (VARD), and percutaneous drainage
- Endoscopic Approach: This involves transgastric or transduodenal drainage using self-expanding metal stents (lumen-apposing metal stents), with or without plastic stents, and direct endoscopic necrosectomy
- Transcutaneous Drainage Approach: This involves percutaneous methods
- Open Surgical Approach: This is the least preferred due to a higher rate of complications compared to minimally invasive methods

Preferred Treatment Approach

- The American Gastroenterological Association (AGA) recommends endoscopic drainage or transcutaneous drainage as first-line treatments for infected necrosis
- Endoscopic drainage is preferred because it avoids potential complications such as pancreatico-cutaneous fistula
- Transcutaneous drainage is suitable for patients with early necrosis (< 2 weeks) or those too ill to undergo endoscopy

Scanned with CamScanner

Comparative Studies on Necrosectomy Techniques

- A randomized trial showed that step-up therapy (starting with antibiotics and percutaneous catheter drainage, followed by minimally invasive surgery such as VARD) was as effective as open surgical approaches for infected necrosis. Patients undergoing step-up therapy had lower mortality and fewer complications after a mean follow-up of 86 months
- Multiple trials have compared endoscopic transluminal drainage with or without necrosectomy to minimally invasive

Pancreatic Necrosis Management

Early Enteral Feeding

- Initiate enteral feeding early in the course of pancreatic necrosis to reduce the risk of infected necrosis

Sterile Necrosis Management

- Most patients with sterile necrosis improve with supportive care alone
- Surgical or endoscopic debridement is indicated if there are persistent symptoms such as nausea, vomiting, abdominal pain, or inability to tolerate an oral diet

Prophylactic Antibiotics

- The routine use of prophylactic antibiotics to prevent infected necrosis is not recommended

Infected Necrosis Management

- Patients with infected necrosis require drainage and/or debridement
- In clinically stable patients, supportive care with intravenous antibiotics for at least four weeks is recommended before attempting definitive management. This period allows the necrotic collection to mature, liquefy, and become walled off, facilitating easier debridement
- Routine use of antifungal agents is not recommended

Debridement and Drainage Options

- Minimally Invasive Surgical Approach: This includes laparoscopic drainage and necrosectomy, video-assisted retroperitoneal debridement (VARD), and percutaneous drainage (Foley et al., 2009).
- Endoscopic Approach: This involves transgastric or transduodenal drainage using self-expanding metal stents (lumen-apposing metal stents), with or without plastic stents, and direct endoscopic necrosectomy
- Transcutaneous Drainage Approach: This involves percutaneous methods
- Open Surgical Approach: This is the least preferred due to a higher rate of complications compared to minimally invasive methods

Preferred Treatment Approach

- The American Gastroenterological Association (AGA) recommends endoscopic drainage or transcutaneous drainage as first-line treatments for infected necrosis

Scanned with CamScanner

- Endoscopic drainage is preferred because it avoids potential complications such as pancreatico-cutaneous fistula
- Transcutaneous drainage is suitable for patients with early necrosis (< 2 weeks) or those too ill to undergo endoscopy

Comparative Studies on Necrosectomy Techniques

- A randomized trial showed that step-up therapy (starting with antibiotics and percutaneous catheter drainage, followed by minimally invasive surgery such as VARD) was as effective as open surgical approaches for infected necrosis. Patients undergoing step-up therapy had lower mortality and fewer complications after a mean follow-up of 86 months
- Multiple trials have compared endoscopic transluminal drainage with or without necrosectomy to minimally invasive surgical approaches (e.g., percutaneous drainage, VARD, laparoscopic cystogastrostomy, and necrosectomy). The MISER and TENSION trials found that both approaches were similar in terms of effectiveness, mortality, development of organ failure, bleeding, and perforation
- There was, however, a higher incidence of pancreatic fistulae in the minimally invasive surgical approach (MISER: 28%, TENSION: 32%) compared to the endoscopic approach (MISER: 0%, TENSION: 5%)

Other Complications

Splanchnic Vein Thrombosis

- Splanchnic vein thrombosis (affecting the splenic vein, portal vein, and mesenteric veins) occurs in up to 20% of patients with acute necrotizing pancreatitis
- The overall course is usually benign, and complications are uncommon
- Treatment focuses on managing the underlying pancreatitis, although short-term anticoagulation may be used in patients with portal or mesenteric vein thrombosis

Scanned with CamScanner

CHRONIC PANCREATITIS

Definition

- Chronic pancreatitis is a long-standing inflammation of the pancreas that leads to irreversible damage, characterized by fibrosis, loss of pancreatic function, and chronic abdominal pain. It results in the progressive decline of both exocrine and endocrine functions, often leading to digestive issues and diabetes mellitus. Common causes include long-term alcohol abuse, smoking, genetic predispositions, and autoimmune conditions

Etiology of Chronic Pancreatitis (CP) Chronic pancreatitis (CP) is a multifactorial disease with various etiologies and risk factors contributing to its development. Understanding these underlying causes is crucial for accurate diagnosis, effective treatment, and prevention. Here, we explore the major etiologies and risk factors associated with CP.

Alcohol Consumption

- Alcohol consumption is the most significant risk factor for chronic pancreatitis, accounting for 70%-90% of all cases
    - Alcohol Intake:
        - Threshold: At least 5 years of alcohol intake exceeding 150 grams per day is typically required to develop CP
        - Prevalence: Despite heavy alcohol consumption being a major risk factor, only 10-20% of heavy drinkers develop CP. This indicates that additional factors, such as genetic predispositions and environmental influences, play a role in disease development
        - Mechanism: Alcohol induces oxidative stress, toxic metabolite production, and changes in pancreatic ductal cells, leading to inflammation, fibrosis, and eventually chronic pancreatitis
    - Smoking as a Cofactor:
        - Role: Smoking significantly exacerbates the risk of developing CP in individuals who consume alcohol heavily. It acts synergistically with alcohol, accelerating the pathogenesis of the disease
        - Impact: Studies have shown that smoking increases the risk of CP and can worsen the prognosis for patients with alcoholic CP
    - Primary Painless Chronic Pancreatitis:
        - Characteristics: Less than 10% of patients with alcoholic CP present without significant pain, a condition known as primary painless chronic pancreatitis
        - Implications: The absence of pain can delay diagnosis and treatment, leading to more severe disease progression

Scanned with CamScanner

Genetic Mutations

- Genetic factors play a crucial role in the development of chronic pancreatitis, particularly in patients without significant alcohol intake. Various genetic mutations have been linked to CP, providing insights into the hereditary aspects of the disease (Whitcomb, 2004).
    - Key Genetic Mutations:
- PRSS1 (Protease, Serine 1): Mutations in this gene, which encodes the enzyme trypsinogen, can lead to hereditary pancreatitis. These mutations cause premature activation of trypsinogen within the pancreas, resulting in autodigestion and chronic inflammation
- SPINK1 (Serine Peptidase Inhibitor, Kazal Type 1): Mutations in the SPINK1 gene, which encodes a trypsin inhibitor, reduce the pancreas's ability to inhibit prematurely activated trypsin, contributing to chronic pancreatitis
- CFTR (Cystic Fibrosis Transmembrane Conductance Regulator): Mutations in the CFTR gene, associated with cystic fibrosis, can also lead to chronic pancreatitis. These mutations affect the pancreatic ducts' chloride and bicarbonate transport, leading to thickened secretions and ductal obstruction
- CPA1 (Carboxypeptidase A1): Mutations in the CPA1 gene, which encodes an enzyme involved in protein digestion, have been implicated in chronic pancreatitis
- CLDN2 (Claudin-2): Variants in the CLDN2 gene, which encodes a protein involved in tight junctions between cells, have been linked to an increased risk of CP

Other Etiological Factors Beyond alcohol consumption and genetic mutations, several other factors contribute to the development of chronic pancreatitis:

- Idiopathic Pancreatitis:
    - Definition: Idiopathic pancreatitis refers to cases where no obvious cause is identified. It can be further categorized into early-onset and late-onset idiopathic pancreatitis
    - Characteristics: Patients with idiopathic CP often have a genetic predisposition or environmental factors that are not fully understood
- Autoimmune Pancreatitis:
    - Description: This is a form of chronic pancreatitis caused by an autoimmune response against the pancreas (Okazaki et al., 2008).
    - Symptoms: It often presents with pancreatic enlargement, jaundice, and elevated serum IgG4 levels (Okazaki et al., 2008).
    - Treatment: Steroids are effective in treating autoimmune pancreatitis, distinguishing it from other forms of CP
- Obstructive Pancreatitis:
    - Causes: Obstructive pancreatitis can result from structural abnormalities such as pancreatic duct strictures, tumors, or congenital anomalies like pancreas divisum
    - Mechanism: These obstructions lead to impaired pancreatic drainage, increased ductal pressure, and subsequent inflammation and fibrosis
- Hyperlipidemia:
    - Association: Elevated levels of lipids in the blood, particularly triglycerides, are associated with an increased risk of pancreatitis

Scanned with CamScanner

- Mechanism: Hyperlipidemia leads to the accumulation of free fatty acids in the pancreas, causing inflammation and injury

- Hypercalcemia:
  - Link: Chronic hypercalcemia, often due to hyperparathyroidism, is a recognized risk factor for CP
  - Mechanism: High calcium levels can lead to pancreatic ductal calcifications and activation of digestive enzymes within the pancreas

TIGAR-O System Classification of Chronic Pancreatitis Etiologies

Category	Etiology	Description
Toxic-Metaboli c	Alcohol, Smoking, Hypercalcemia, Hyperlipidemia and Certain medications	Chronic alcohol consumption leading to direct pancreatic damage, Smoking, which exacerbates the effects of other risk factors? Elevated calcium levels causing pancreatic enzyme activation and damage. High lipid levels in the blood leading to recurrent pancreatic inflammation. Medications such as diuretics, corticosteroids, and some antibiotics causing pancreatic inflammation
Idiopathic	Tropical pancreatitis	Chronic pancreatitis prevalent in tropical regions, often with nutritional deficiencies.
Genetic	Hereditary pancreatitis, CFTR mutations and SPINK1 mutations	Genetic mutations passed down in families, leading to early-onset pancreatitis. Mutations in the CFTR gene associated with cystic fibrosis and pancreatic insufficiency. Mutations in the SPINK1 gene leading to reduced protection against trypsin activity in the pancreas
Autoimmune	IgG4-related disease and Other autoimmune conditions	Autoimmune attack on the pancreas, leading to inflammation and fibrosis. Other autoimmune diseases that secondarily affect the pancreas.
Recurrent and Severe Pancreatitis	Post-necrotic, Post-traumatic and Severe acute pancreatitis episodes	Pancreatitis resulting from previous episodes of severe acute pancreatitis. Pancreatic damage following physical injury to the abdomen. Repeated episodes of acute pancreatitis causing chronic inflammation and damage.
Obstructive	Pancreatic duct obstruction, Tumors and Congenital abnormalities	Blockages in the pancreatic ducts leading to backpressure and damage. Tumors causing obstruction and subsequent pancreatic damage. Congenital anomalies such as pancreas divisum causing pancreatic duct obstruction.

Scanned with CamScanner

Diagnosis of Chronic Pancreatitis (CP)

Chronic pancreatitis (CP) is a long-standing inflammation of the pancreas that alters its normal structure and functions. Diagnosing CP can be challenging, particularly in its early stages, because symptoms and imaging findings may not be specific. A combination of functional and structural tests is often required to accurately diagnose and assess the severity of the disease. Here we delve into the details of these diagnostic methods.

Functional Tests

Functional tests evaluate the exocrine function of the pancreas, specifically its ability to produce digestive enzymes and bicarbonate.

1. **72-Hour Fecal Fat Collection:**
   - **Purpose:** This test measures the amount of fat excreted in the stool over a 72-hour period. It's considered a gold standard for detecting fat malabsorption, a common consequence of pancreatic insufficiency
   - **Procedure:** The patient follows a high-fat diet (100 grams per day) for a few days before and during the stool collection period. The collected stool is then analysed for fat content.
   - **Criteria:** An excretion of more than 7 grams of fat per 24 hours is considered abnormal and indicative of malabsorption.
2. **Spot Fecal Fat (Sudan Staining):**
   - **Purpose:** This qualitative test detects the presence of fat in a stool sample using Sudan III stain
   - **Procedure:** A small sample of stool is mixed with Sudan III dye, and the presence of fat globules is observed under a microscope.
   - **Criteria:** This test is less sensitive and only detects fat if excretion is greater than or equal to 25 grams per 24 hours, making it less useful for diagnosing early-stage CP.
3. **Fecal Elastase:**
   - **Purpose:** Fecal elastase is an enzyme produced by the pancreas. Measuring its concentration in stool helps assess pancreatic exocrine function (Lowe et al., 2009).
   - **Procedure:** A single stool sample is analysed for elastase concentration using immunoassays.
   - **Criteria:** Levels below 100 micrograms per gram of stool are considered abnormal and suggest exocrine pancreatic insufficiency.
4. **Serum Trypsin:**
   - **Purpose:** Trypsin is another enzyme produced by the pancreas, and its levels in the blood reflect pancreatic enzyme output
   - **Procedure:** A blood sample is taken and analysed for trypsin concentration.
   - **Criteria:** Levels below 20 nanograms per milliliter are considered abnormal and indicate reduced pancreatic function.
5. **Secretin Stimulation Test (Double Tube Test):**
   - **Purpose:** This test evaluates the pancreas's ability to produce bicarbonate in response to secretin, a hormone that stimulates pancreatic secretion

Scanned with CamScanner

- **Procedure:** The patient undergoes intubation with nasogastric and nasoduodenal tubes to collect gastric and duodenal secretions. Secretin is administered intravenously, and the peak bicarbonate concentration in the duodenal fluid is measured.
- **Criteria:** A peak bicarbonate concentration of less than 80 milliequivalents per liter is considered abnormal.
- **Sensitivity and Specificity:** The test has a sensitivity of 75% for early CP and 97% for late CP, with a specificity of 90%.
- **Notes:** Although this test is more sensitive than imaging studies for early CP, it is invasive, time-consuming, and unpleasant for the patient. It is also only available in specialized centers

Structural Tests

Structural tests provide imaging of the pancreas to identify morphological changes associated with chronic pancreatitis. These tests are generally more sensitive for detecting late-stage disease.

1. **Computed Tomography (CT) Scan:**
   - **Purpose:** CT scans are commonly used as the first-line imaging modality for diagnosing CP. They provide detailed images of the pancreas, revealing structural abnormalities such as calcifications, ductal dilation, and atrophy
   - **Procedure:** The patient undergoes a CT scan, where X-rays are used to create cross-sectional images of the pancreas.
   - **Findings:** CT can detect calcifications, pseudocysts, and changes in the size and shape of the pancreas, which are indicative of chronic pancreatitis
2. **Magnetic Resonance Imaging (MRI):**
   - **Purpose:** MRI provides high-resolution images of the pancreas and is particularly useful for visualizing soft tissue changes and ductal structures (Bakker et al., 2007).
   - **Procedure:** The patient undergoes an MRI scan, which uses magnetic fields and radio waves to create detailed images.
   - **Findings:** MRI can detect pancreatic atrophy, fibrosis, and ductal irregularities. Magnetic Resonance Cholangiopancreatography (MRCP), a specific type of MRI, can visualize the pancreatic and bile ducts without the need for contrast agents
3. **Endoscopic Ultrasound (EUS):**
   - **Purpose:** EUS is an advanced imaging technique that provides detailed images of the pancreas and surrounding structures. It is particularly useful when CT or MRI findings are inconclusive
   - **Procedure:** An endoscope equipped with an ultrasound probe is inserted through the mouth into the stomach and duodenum, allowing close proximity imaging of the pancreas.
   - **Findings:** EUS can detect subtle changes such as early fibrosis, small ductal changes, and pancreatic lesions that might not be visible on CT or MRI

Scanned with CamScanner

Combining Functional and Structural Tests

Diagnosing chronic pancreatitis often requires a combination of functional and structural tests to provide a comprehensive assessment of pancreatic health. The choice of tests depends on the clinical presentation, the stage of the disease, and the resources available.

- **Early-Stage CP:** Functional tests like the secretin stimulation test and fecal elastase measurement are more sensitive for detecting early exocrine insufficiency. EUS can provide detailed images of subtle structural changes
- **Late-Stage CP:** Structural tests like CT and MRI are more effective at identifying the extensive morphological changes characteristic of advanced chronic pancreatitis. Functional tests can confirm the severity of exocrine insufficiency

Endoscopic Ultrasound (EUS) Criteria for Diagnosing Chronic Pancreatitis According to the Rosemont Classification

Criteria	Description	Diagnosis
Major criteria		
Major A		Consistent with chronic pancreatitis
Hyperechoic foci with shadowing	Bright echoes with shadowing indicating calcifications	1 major A feature + ≥ 3 minor features
Main pancreatic duct (PD) calculi	Presence of stones in the main pancreatic duct	1 major A feature + major B feature
Major B		2 major A features
Lobularity with honeycombing	Cluster of lobules with an echogenic outline	Suggestive of chronic pancreatitis
Minor criteria		
Cysts	Anechoic structures within the pancreas	1 major A feature + < 3 minor features
Dilated ducts ≥ 3.5 mm	Main duct diameter greater than 3.5 mm	1 major B feature + ≥ 3 minor features
Irregular PD contour	Irregular course of the main duct	≥ 5 minor features (any)
Dilated side branches ≥ 1 mm	Side branches of the duct larger than 1 mm	Indeterminate for chronic pancreatitis
Hyperechoic duct wall	Bright walls of the duct	3 to 4 minor features, no major features
Hyperechoic strands	Bright, linear echoes without shadowing	Major B feature alone or with < 3 minor features
Nonshadowing hyperechoic foci	Bright echoes without shadowing indicating fibrosis	Normal
Lobularity with non-contiguous lobules	Cluster of lobules without an echogenic outline	≤ 2 minor features, no major features

Scanned with CamScanner

Comprehensive Treatment Guidelines for Chronic Pancreatitis (CP)

Confirming the Diagnosis

- **Patient History:** A thorough review of the patient's medical history is crucial. This includes documenting the symptoms, their duration, any exacerbating or alleviating factors, and previous treatments or interventions. Chronic Pancreatitis typically presents with persistent abdominal pain, digestive issues, and sometimes diabetes
- **Diagnostic Tests:** Diagnostic confirmation relies on a combination of imaging studies and pancreatic function tests. Common imaging modalities include CT scans, MRI, and Endoscopic Ultrasound (EUS), which can reveal calcifications, ductal irregularities, and other structural abnormalities in the pancreas. Pancreatic function tests assess exocrine function and can help confirm the diagnosis

Assessing Risk Factors

- **Modifiable Risk Factors:** Identifying and addressing risk factors is essential for managing CP. Key modifiable risk factors include:
  - **Alcohol Consumption:** Excessive alcohol intake is a significant risk factor for CP. Patients should be strongly encouraged to abstain from alcohol
  - **Smoking:** Smoking cessation is vital as it exacerbates the condition and increases the risk of pancreatic cancer. Provide resources and support for quitting

Ruling out Treatable Complications

- **Pancreatic Pseudocyst:** These fluid collections can be detected via imaging and may require drainage if symptomatic or infected
- **Duodenal Obstruction:** Evaluate for signs of duodenal obstruction or narrowing, which can cause significant symptoms and complications
- **Bile Duct Obstruction:** Assess for any blockages or strictures in the bile ducts that could lead to jaundice and biliary complications
- **Malignancy:** It's crucial to rule out pancreatic cancer or other malignancies, particularly in patients with new-onset diabetes or significant weight loss

Considering Other Causes of Pain

- **Peptic Ulcer Disease:** Rule out ulcers through endoscopy or other appropriate testing, as these can mimic the pain of CP
- **Gastroparesis:** Consider this condition if there are symptoms of delayed gastric emptying, such as bloating, nausea, and vomiting

Lifestyle Modifications

- **Alcohol Abstinence:** Strongly encourage patients to abstain from alcohol, providing counseling and support to aid in cessation

Scanned with CamScanner

- **Smoking Cessation:** Advise quitting smoking and offer resources, including nicotine replacement therapies and smoking cessation programs

Nutritional and Genetic Testing

- **Vitamin Levels:** Test for deficiencies in fat-soluble vitamins (A, E, D, K), which are common in CP patients due to malabsorption
- **Genetic Testing:** For CP of unknown etiology, especially in patients younger than 35, genetic testing is recommended to identify any hereditary factors contributing to the condition

Medical Therapy for Pain Management

- **Referral to Pain Clinic:** Consider referring the patient to a specialized pain clinic for comprehensive pain management and treat any coexisting depression
- **Analgesics:** First-line analgesics include acetaminophen, NSAIDs, and tramadol. Use narcotics cautiously due to the high risk of addiction

Non-Enteric Coated Pancreatic Enzyme Therapy

- **Mechanism of Action:** One proposed mechanism of pain in CP is increased intrapancreatic pressure. Ingestion of food induces the production of cholecystokinin-releasing factor (CCK-RF) in the duodenum, which stimulates the release of CCK. CCK, in turn, stimulates the secretion of pancreatic enzymes, increasing pancreatic pressure and pain
- **Exogenous Enzymes:** Administering exogenous pancreatic enzymes denatures CCK-RF, limiting CCK release and therefore decreasing pain
- **Guidelines:** Despite this mechanism, the ACG 2020 guidelines do not recommend pancreatic enzyme supplementation for pain treatment in CP due to expense and lack of efficacy

Endoscopic Therapy

- **Goal:** The primary aim is to improve pancreatic drainage and thus decrease intrapancreatic pressure
- **Ideal Candidates:** Patients with pancreatic duct stones or strictures in the head of the pancreas with upstream ductal dilation are ideal candidates for endoscopic therapy
- **Techniques:** These include pancreatic sphincterotomy, stricture dilation, and stone extraction with or without stent placement (7-10 French) in the pancreatic duct
- **ESWL:** External Shock Wave Lithotripsy (ESWL) is beneficial for large pancreatic stones (>5 mm). Studies indicate ESWL alone can be as effective as a combined approach of ESWL and endoscopic therapy in patients with painful CP and calcifications obstructing the main pancreatic duct

Celiac Plexus Block

Scanned with CamScanner

- **Procedure:** This involves injecting a local anesthetic with or without steroids around the celiac plexus, which can be performed percutaneously or endoscopically through EUS. This method provides short-term pain relief (2-4 months)

Surgical Therapy

- **Lateral Pancreaticojejunostomy (Puestow Procedure):** This surgery is considered for patients with a dilated pancreatic duct (>5 mm)
- **Other Surgeries:** These include pancreaticoduodenectomy (Whipple procedure), pancreatic head resection combined with drainage (Berger and Frey procedures), or total pancreatectomy with islet autotransplantation

Comparative Studies

- **Endoscopic vs. Surgical Therapy:** Review studies comparing these treatment approaches to determine the best option for individual patients. Endoscopic therapy is less invasive but may be less effective long-term compared to surgical options, which might provide more definitive relief for certain patients

Complications of Chronic Pancreatitis (CP)

- **Pancreatic Pseudocyst:** A pancreatic pseudocyst is a peripancreatic fluid collection that develops more than four weeks after acute pancreatitis, characterized by a well-defined wall. It forms due to pancreatic duct (PD) disruption and inflammation
    - **Management:**
        - **Asymptomatic Cysts:** Consider watchful waiting and repeat imaging every 3-6 months.
        - **Drainage Options:** Endoscopic drainage, percutaneous drainage, or surgical drainage depending on the size and symptoms
- **Duodenal Obstruction:** This results from inflammation in the pancreatic head or a large pseudocyst. Management options include pseudocyst drainage and gastrojejunostomy
- **Common Bile Duct (CBD) Strictures:** CBD strictures are commonly due to inflammation and fibrosis around the intrapancreatic portion of the CBD. Other causes include compression from a pseudocyst, choledocholithiasis, or malignancy
    - **Treatment:** ERCP with balloon dilation and stenting is the treatment of choice
- **Pancreatic Leak and Fistula Formation:** Leakage of pancreatic fluid can lead to pancreatic ascites, pleural effusion, and rarely pericardial effusion
    - **Treatment:** Conservative management, ERCP with PD stent, or surgical resection and drainage for refractory cases
- **Splenic Vein Thrombosis:** This develops secondary to local inflammation or extrinsic compression from a pseudocyst, leading to portal hypertension and gastric varices. Treatment includes splenectomy for gastric variceal bleeding
- **Pseudoaneurysm:** Aneurysms develop due to inflammation and partial digestion of an arterial wall, leading to aneurysmal dilation
    - **Treatment:** Angiography and embolization are the primary treatments. Surgical resection is necessary for refractory cases

Scanned with CamScanner

- **Pancreatic Exocrine Insufficiency:** Steatorrhea develops when there is less than 10% of functioning pancreatic exocrine glands
    - **Treatment:** Pancreatic enzyme replacement therapy with regular monitoring
- **Endocrine Dysfunction:** Screening for diabetes is recommended annually in patients with CP. Treatment includes metformin for mild hyperglycemia and insulin for more severe cases
- **Metabolic Bone Disease:** Osteopenia and osteoporosis are common in patients with CP.
    - **Screening and Treatment:** Baseline screening (DEXA scan), vitamin D and calcium supplements, and lifestyle modifications
- **Pancreatic Cancer:** The risk of pancreatic adenocarcinoma is increased in CP
    - **Risk:** Cumulative risk is around 1.8% after 10 years and 4% after 20 years of follow-up. Smoking further increases this risk

Scanned with CamScanner

AUTOIMMUNE PANCREATITIS (AIP)

Definition

Autoimmune pancreatitis (AIP) is a rare form of chronic pancreatitis characterized by an autoimmune inflammatory process within the pancreas. This condition is distinguished by a prominent lymphoplasmacytic infiltrate (infiltration of the pancreas by lymphocytes and plasma cells) and fibrosis (formation of excess fibrous connective tissue)

Subtypes

There are two primary subtypes of AIP:

1. **Type 1 AIP (Lymphoplasmacytic Sclerosing Pancreatitis):** Often associated with elevated levels of serum IgG4 and systemic involvement (IgG4-related disease)
2. **Type 2 AIP (Idiopathic Duct-Centric Pancreatitis):** Typically confined to the pancreas, often associated with inflammatory bowel disease, and not usually linked to elevated serum IgG4 levels

Diagnosis

The diagnosis of AIP is multifaceted and based on the HISORt criteria from the Mayo Clinic. These criteria encompass Histopathology, Imaging features, Serology, Other organ involvement, and Response to steroid therapy

Histopathology:

- **Gold Standard:** Histological examination of pancreatic tissue is the definitive diagnostic tool. Typical findings include a dense lymphoplasmacytic infiltrate, storiform fibrosis (whorled pattern of fibrosis), and obliterative phlebitis (vein inflammation and obstruction by fibrosis)
- **EUS-FNA (Endoscopic Ultrasound-Guided Fine Needle Aspiration):** While useful for ruling out malignancy, EUS-FNA often provides insufficient tissue for a definitive AIP diagnosis. An EUS-core biopsy is required to capture the full spectrum of pathological features

Imaging Features:

- **Typical Features:** These include a diffusely enlarged pancreas (sausage-shaped) with a hypo-enhancing capsule-like rim and no pancreatic ductal dilation
- **Atypical Features:** Focal pancreatic enlargement may be present. An abrupt cut off of the pancreatic duct with upstream atrophy strongly suggests malignancy rather than AIP

Serology:

- **IgG4 Levels:** Elevated serum IgG4 levels ($\geq$ 2 times the ULN) support an AIP diagnosis, though lower levels do not exclude the condition. Elevated IgG4 can also occur in about 10% of pancreatic cancer cases, and 1% of these patients may have levels $\geq$ 2 times ULN. Elevated CA 19-9 can also be observed in AIP

Scanned with CamScanner

Other Organ Involvement:

- **Association with Other Organs:** AIP can be associated with involvement in other organs such as the bile ducts, kidneys, salivary glands, and lymph nodes, consistent with IgG4-related disease

Response to Steroid Therapy:

- **Steroid Trial:** Treat with steroids and reassess pancreatic imaging and IgG4 levels in 4 weeks. Objective improvement in imaging and a decrease in IgG4 levels suggest AIP
- **Clinical Symptoms:** Improvement in clinical symptoms is helpful but not definitive for AIP as symptom relief can occur in other conditions too

Treatment

Initial Treatment:

- **Prednisone:** Start with prednisone 40 mg (or 0.6-1.0 mg/kg/day) for 4 weeks. Assess the response at 4 weeks by evaluating clinical symptoms, liver enzymes, IgG4 levels, and radiologic findings. If there is a favourable response, taper the steroids by 5 mg per week

Rituximab:

- **Indication:** Rituximab, a monoclonal antibody that depletes B cells, is effective in inducing remission in AIP. It is given in two doses of 1000 mg, two weeks apart. Rituximab is recommended as first-line therapy for patients who cannot tolerate steroids or are at high risk of relapse

Management of Relapse:

- **Incidence:** Relapse occurs in up to 60% of patients with Type 1 AIP (Yamamoto et al., 2012).
- **Predictors of Relapse:** Key predictors include diffuse pancreatic enlargement, delayed radiological response, persistent elevation of IgG4 (>2x ULN) post-treatment, involvement of multiple organs with IgG4 disease, and proximal biliary IgG4-SC strictures
- **Maintenance Therapy:** For patients at high risk of relapse, maintenance therapy with low-dose steroids (5-7.5 mg/day), immunomodulators (azathioprine or mycophenolate mofetil), or Rituximab is recommended. A randomized controlled trial demonstrated that low-dose corticosteroids significantly reduced the 3-year relapse rate from 57.9% to 23.3% (Ito et al., 2015).

Persistent or Non-Responders:

- **Treatment:** Patients who relapse on steroids or do not respond to steroids should be treated with Rituximab

Scanned with CamScanner

Type 2 AIP:

- **Relapse:** Relapse is uncommon in Type 2 AIP. If relapse occurs, treat with repeat steroids

Severe Jaundice and/or Cholangitis:

- **ERCP:** In cases of severe jaundice and/or cholangitis, Endoscopic Retrograde Cholangiopancreatography (ERCP) with stenting, brushing, and biopsy is indicated to relieve the obstruction and obtain tissue for diagnosis.

- Detailed Subtypes and Characteristics of Autoimmune Pancreatitis

Feature	Type 1 AIP (IgG4-Related)	Type 2 AIP (Idiopathic Duct-Centric)
Age of Onset	- Typically affects older adults. - Mean age of onset: 60-70 years. - Rarely seen in individuals under 50.	- Typically affects younger individuals. - Mean age of onset: 40-50 years. - Can occur in adolescents.
Gender Predominance	- Predominantly affects males. - Male to female ratio approximately 3:1. - Consistent across different populations.	- No clear gender predominance. - Affects males and females almost equally. - Slight female predominance in some studies.
Histology	- Characterized by lymphoplasmacytic sclerosing pancreatitis (LPSP). - Dense infiltration of lymphocytes and IgG4-positive plasma cells. - Storiform fibrosis (a swirling pattern of fibrosis).	- Marked by idiopathic duct-centric pancreatitis (IDCP). - Granulocytic epithelial lesions. - Duct-centric inflammation without IgG4-positive plasma cells.
Serum IgG4 Levels	- Elevated in most cases. - Serves as a useful diagnostic marker. - Levels can be more than twice the normal upper limit.	- Usually normal. - Not helpful in diagnosis. - IgG4 levels typically within the normal range.
Other Organ Involvement	- Frequently involves other organs (salivary glands, kidneys, lungs, bile ducts). - Indicative of systemic IgG4-related disease. - Multisystem involvement common	- Rarely involves other organs. - Usually confined to the pancreas - Minimal extra pancreatic manifestations
Histopathology Findings	- Dense lymphoplasmacytic infiltration - Storiform fibrosis - Obliterative phlebitis	- Granulocytic epithelial lesions - Inflammation centered around the ducts - No significant fibrosis

Scanned with CamScanner

	(inflammation of veins)	
Response to Steroids	- Generally shows a good response to steroid therapy. - Significant clinical improvement is common. - Steroid-sparing agents may be needed for long-term management.	- Responds well to steroids. - Notable reduction in inflammation - Relapse can occur but less frequently than Type 1.
Recurrence after Treatment	- Recurrences are common. - Requires long-term monitoring - Sometimes necessitates maintenance therapy with immunosuppressants	- Less common recurrence - Many patients achieve prolonged remission. - Regular follow-up still recommended.
Association with Inflammatory Bowel Disease	- Rarely associated with inflammatory bowel diseases - Low incidence of concomitant conditions - Can occur independently of bowel disease	- Frequently associated with inflammatory bowel diseases (especially ulcerative colitis). - High prevalence of concomitant conditions. - Often diagnosed in patients with pre-existing bowel disease.
Imaging Findings	- Diffuse or focal pancreatic enlargement. - Characteristic 'sausage-shaped' appearance of the pancreas. - Delayed enhancement on imaging studies.	- Segmental or focal enlargement of the pancreas. - Lacks characteristic shape seen in Type 1. - May show strictures in pancreatic duct.
Diagnostic Markers	- High serum IgG4 levels. - Biopsy showing abundant IgG4-positive plasma cells are key diagnostic markers. - Other supportive markers include elevated IgE and eosinophils.	- No specific serologic markers available. - Diagnosis relies on biopsy showing duct-centric inflammation. - Imaging and clinical features critical for diagnosis.
Common Symptoms	- Jaundice. - Abdominal pain. - Weight loss. - Diabetes.	- Abdominal pain. - Acute episodes of pancreatitis. - Often without jaundice or weight loss. - May present with recurrent episodes.

Scanned with CamScanner

PANCREATIC ADENOCARCINOMA

- **Prevalence:**
  - In the United States, pancreatic cancer remains a significant health issue, with the estimated incidence for 2020 being approximately 57,600 new cases. This highlights the growing concern regarding this malignancy and the need for effective diagnostic and therapeutic strategies.
- **Survival Rates:**
  - Pancreatic adenocarcinoma is notorious for its poor prognosis. The overall five-year survival rate across all stages of the disease is a mere 9%. This stark statistic underscores the aggressive nature of the disease and the challenges associated with its management.
- **Mortality:**
  - This type of cancer is the fourth leading cause of cancer-related deaths in the United States. In 2020 alone, it was responsible for an estimated 47,050 fatalities. The high mortality rate is closely tied to the late-stage diagnosis, which is often when the disease is first detected.
- **Lifetime Risk:**
  - The estimated lifetime risk of developing pancreatic cancer is 1.7%. This relatively low percentage still translates into a significant number of individuals affected, given the population size, making it a critical area of focus for oncologists and researchers.

Diagnosis and Disease Stage

- **Late Presentation:**
  - One of the primary challenges in managing pancreatic adenocarcinoma is its typically late presentation. At the time of diagnosis, 52% of patients already have distant metastatic disease, which severely limits treatment options and adversely affects prognosis.
- **Localized Disease:**
  - Only 10% of patients have localized disease at the time of diagnosis. Early detection in these cases offers the best chance for effective treatment and improved survival rates, but such cases are unfortunately rare.

Risk Factors

Demographic Factors

- **Gender:**
  - Males are at a higher risk of developing pancreatic adenocarcinoma compared to females.
- **Age:**
  - The risk of developing pancreatic cancer increases with age, with most cases diagnosed in individuals over the age of 60.

Lifestyle and Health-Related Factors

Scanned with CamScanner

- **Obesity:**
  - Obesity is a significant risk factor for pancreatic cancer, with higher body mass index (BMI) being correlated with an increased risk.
- **Smoking:**
  - Tobacco use is a well-established risk factor, significantly elevating the risk of pancreatic cancer.
- **Chronic Conditions:**
  - Chronic pancreatitis and cystic fibrosis are associated with an increased risk of pancreatic adenocarcinoma. Long-standing diabetes also contributes to the elevated risk.
- **Family History:**
  - A family history of pancreatic cancer, especially in a first-degree relative, is a notable risk factor, highlighting the role of genetic predisposition.

Genetic and Hereditary Factors

- **Precursor Lesions:**
  - Pancreatic adenocarcinoma can develop from precursor lesions such as pancreatic intraepithelial neoplasia (PanIN), intraductal papillary mucinous neoplasm (IPMN), and mucinous pancreatic cysts. Monitoring and managing these lesions is crucial for early detection and prevention.
- **IPMN:**
  - Patients with IPMN need to be carefully monitored as they are at risk of developing pancreatic adenocarcinoma in regions of the pancreas distinct from the initial cystic area.

Genetic Testing and Screening

Genetic Testing Recommendations

- **Guidelines:**
  - The National Comprehensive Cancer Network (NCCN) and the American Society of Clinical Oncology (ASCO) recommend germline testing for all patients with confirmed pancreatic adenocarcinoma. This involves using comprehensive gene panels to identify hereditary cancer syndromes.
- **Importance:**
  - Identifying genetic mutations can inform patient management, guide treatment decisions, and help assess familial risk.

Screening and Monitoring

- **High-Risk Populations:**
  - Screening is particularly important for high-risk populations, including individuals with a family history of pancreatic cancer or associated hereditary syndromes.
- **Methods:**

Scanned with CamScanner

- Screening guidelines recommend the use of imaging and genetic testing to identify individuals at heightened risk. This can facilitate early detection and intervention, which are critical for improving survival rates.

- **Precursor Lesions Monitoring:**
- Vigilant monitoring of patients with precursor lesions such as IPMN is essential. These patients need regular follow-ups to detect any progression towards malignancy, ensuring timely and effective intervention.

Syndromes Predisposing to Pancreatic Cancer and Associated Screening Recommendations Based on Guidelines from the International Cancer of the Pancreas Screening (CAPS) Consortium.

Syndrome	Genetic Mutation	Lifetime Risk of Pancreatic Cancer	Screening for Pancreatic Cancer	Features
Hereditary Breast and Ovarian Cancer Syndrome (HBOC)	BRCA1, BRCA2	5-10%	Consider annual MRI/MRCP and/or endoscopic ultrasound (EUS) starting at age 50 or 10 years earlier than the youngest pancreatic cancer diagnosis in the family.	- Increased risk of breast, ovarian, pancreatic, and prostate cancers. - Autosomal dominant inheritance. - Genetic testing recommended for individuals with a family history.
Lynch Syndrome (Hereditary Nonpolyposis Colorectal Cancer, HNPCC)	MLH1, MSH2, MSH6, PMS2, EPCAM	3-5%	Consider annual MRI/MRCP and/or EUS starting at age 40 or 10 years earlier than the youngest pancreatic cancer diagnosis in the family.	- Increased risk of colorectal, endometrial, ovarian, stomach, small intestine, hepatobiliary tract, urinary tract, brain, and pancreatic cancers. - Autosomal dominant inheritance. - Microsatellite instability (MSI) and mismatch repair deficiency (MMR).
Peutz-Jeghers Syndrome	STK11 (LKB1)	11-36%	Annual MRI/MRCP and/or EUS starting at age 30-35 or 10 years earlier than the youngest pancreatic cancer	- Hamartomatous polyps in the gastrointestinal tract. - Mucocutaneous pigmentation (dark spots on lips, oral mucosa, and digits).

Scanned with CamScanner

			diagnosis in the family.	- Increased risk of cancers, including pancreatic, gastrointestinal, breast, and ovarian cancers. - Autosomal dominant inheritance.
Familial Adenomatous Polyposis (FAP)	APC	1-2%	No established screening guidelines for pancreatic cancer; individual consideration based on family history.	- Numerous adenomatous polyps in the colon and rectum. - Increased risk of colorectal cancer and other cancers, including pancreatic cancer. - Autosomal dominant inheritance. - Prophylactic colectomy often recommended.
Li-Fraumeni Syndrome	TP53	1-2%	No established screening guidelines for pancreatic cancer; individual consideration based on family history.	- Increased risk of various cancers, including sarcomas, breast cancer, brain tumors, adrenocortical carcinoma, and pancreatic cancer. - Autosomal dominant inheritance. - High penetrance with early-onset cancers.
Familial Atypical Multiple Mole Melanoma (FAMMM) Syndrome	CDKN2 A (p16)	10-17%	Consider annual MRI/MRCP and/or EUS starting at age 40 or 10 years earlier than the youngest pancreatic cancer diagnosis in the family.	- Multiple atypical moles and an increased risk of melanoma. - Increased risk of pancreatic cancer. - Autosomal dominant inheritance. - Regular dermatologic and pancreatic screening recommended.
Hereditary Pancreatitis	PRSS1, SPINK1, CFTR	25-40%	Consider annual MRI/MRCP and/or EUS starting at age 30 or 20 years after the onset of pancreatitis.	- Recurrent episodes of acute pancreatitis beginning in childhood or adolescence. - Chronic pancreatitis. - Increased risk of pancreatic cancer. - Autosomal dominant (PRSS1) or autosomal

Scanned with CamScanner

				recessive (SPINK1, CFTR) inheritance.
Ataxia-Telangiectasia	ATM	<1%	No established screening guidelines for pancreatic cancer; individual consideration based on family history.	- Progressive cerebellar ataxia. - Telangiectasias (small dilated blood vessels) in the eyes and skin. - Immunodeficiency. - Increased risk of various cancers, including lymphomas, leukemias, and pancreatic cancer. - Autosomal recessive inheritance.
Von Hippel-Lindau Syndrome	VHL	1-2%	No established screening guidelines for pancreatic cancer; individual consideration based on family history.	- Hemangioblastomas of the brain, spinal cord, and retina. - Renal cell carcinoma. - Pheochromocytoma. - Pancreatic cysts and neuroendocrine tumors. - Autosomal dominant inheritance.
PALB2-Associated Pancreatic Cancer	PALB2	5-10%	Consider annual MRI/MRCP and/or EUS starting at age 50 or 10 years earlier than the youngest pancreatic cancer diagnosis in the family.	- Increased risk of breast and pancreatic cancers. - Autosomal dominant inheritance. - Functionally interacts with BRCA2 in DNA repair.
Multiple Endocrine Neoplasia Type 1 (MEN1)	MEN1	5-10%	Annual MRI/MRCP and/or EUS starting at age 40 or 10 years earlier than the youngest pancreatic cancer diagnosis in the family.	- Tumors of the parathyroid glands, pancreatic islets, and anterior pituitary. - Increased risk of pancreatic neuroendocrine tumors. - Autosomal dominant inheritance. - Regular screening for endocrine tumors recommended.

Scanned with CamScanner

Clinical Manifestations

Symptoms and Physical Findings

- **Common Symptoms:**
  - **Weight Loss and Anorexia:** Significant, unexplained weight loss and loss of appetite are frequent early symptoms.
  - **Abdominal and Back Pain:** Persistent pain in the upper abdomen that may radiate to the back is a common complaint.
  - **Jaundice:** Yellowing of the skin and eyes due to bile duct obstruction is a notable symptom.
  - **Itching:** Associated with jaundice, itching can be a distressing symptom.
  - **Nausea and Vomiting:** Gastrointestinal symptoms such as nausea and vomiting may occur as the disease progresses.
- **Physical Findings:**
  - **Cachexia:** Severe weight loss, muscle atrophy, and general weakness
  - **Jaundice:** Visible yellowing of the skin and eyes
  - **Hepatomegaly:** Enlargement of the liver may be detected on physical examination
- **Other Signs:**
  - **Courvoisier's Sign:** Presence of an enlarged, palpable gallbladder
  - **Trousseau Sign:** Superficial venous thrombosis indicating a hypercoagulable state often associated with malignancy.

Acute Pancreatitis and Pancreatic Cancer

- **Uncommon Presentation:**
  - Acute pancreatitis is an uncommon initial presentation of pancreatic cancer, occurring in approximately 1% of cases.
  - Pancreatic cancer is identified in up to 6% of patients with acute pancreatitis that is not related to alcohol or gallstones.
- **Diagnostic Consideration:**
  - In older patients presenting with acute pancreatitis of unclear etiology, pancreatic cancer should be suspected. High-quality imaging of the pancreas is recommended to rule out malignancy.

Diabetes and Pancreatic Cancer

- **Prevalence:**
  - Diabetes is prevalent in patients with pancreatic adenocarcinoma, affecting around 40% of individuals.
- **New Onset Diabetes:**
  - New onset diabetes in adults, particularly in elderly, non-obese individuals without a family history of diabetes, can be an early manifestation of pancreatic cancer.
  - This type of diabetes often precedes the diagnosis of pancreatic cancer by up to two years.
- **Biomarkers:**

Scanned with CamScanner

- **Vanin-1 and Matrix Metalloproteinase 9:** These biomarkers are associated with pancreatic cancer-related diabetes and m

Diagnosis

Early and accurate diagnosis of pancreatic adenocarcinoma is critical for initiating prompt treatment and improving outcomes:

- **Imaging Modalities:** High-quality contrast-enhanced computed tomography (CT) scans are the primary imaging modality for initial evaluation due to their ability to provide detailed anatomical information and detect pancreatic lesions. Magnetic resonance imaging (MRI) with magnetic resonance cholangiopancreatography (MRCP) and endoscopic ultrasound (EUS) with fine-needle aspiration (FNA) are valuable adjuncts for further characterization of suspicious lesions and obtaining tissue samples for cytological analysis
- **Tumor Markers:** Serum carbohydrate antigen 19-9 (CA 19-9) is the most widely used tumor marker in pancreatic cancer. Elevated CA 19-9 levels correlate with disease burden and response to treatment, although it lacks specificity and can be elevated in benign conditions such as obstructive jaundice

Treatment Strategies

The management of pancreatic adenocarcinoma is guided by disease stage, location, and patient-related factors:

- **Surgical Resection:** Surgical resection offers the only potential for cure in pancreatic cancer. However, only 10-15% of patients present with tumors amenable to curative resection at the time of diagnosis
  - **Whipple Procedure:** Pancreaticoduodenectomy, commonly known as the Whipple procedure, is the standard surgical approach for tumors located in the head of the pancreas. It involves resection of the head of the pancreas, duodenum, distal bile duct, and sometimes a portion of the stomach and proximal jejunum
  - **Borderline Resectable and Unresectable Tumors:** For tumors that are not initially resectable due to vascular involvement (e.g., portal vein encasement), neoadjuvant therapy with chemotherapy or chemoradiotherapy may be employed to downstage the tumor and improve resectability rates
- **Adjuvant Therapy:** Following surgical resection, adjuvant chemotherapy or chemoradiotherapy is administered to reduce the risk of disease recurrence. The regimen typically includes fluoropyrimidine-based chemotherapy (e.g., gemcitabine or 5-fluorouracil) with or without radiotherapy
- **Locally Advanced and Metastatic Disease:** For patients with unresectable locally advanced or metastatic disease, systemic chemotherapy remains the mainstay of treatment. Combination chemotherapy regimens such as FOLFIRINOX (leucovorin, fluorouracil, irinotecan, and oxaliplatin) or gemcitabine plus nab-paclitaxel are commonly used, aiming to prolong survival and improve quality of life
- **Palliative Care:** Symptom management and supportive care play a crucial role in enhancing quality of life for patients with advanced disease. Interventions such as pain

Scanned with CamScanner

control, nutritional support, and psychosocial support are integral components of comprehensive palliative care

Emerging Therapies and Considerations (Recent Advances)

On-going research and clinical trials are exploring novel therapeutic strategies and approaches to improve outcomes in pancreatic adenocarcinoma:

- **Precision Medicine:** Comprehensive genomic profiling and molecular testing of tumors are increasingly utilized to identify specific genetic alterations and potential therapeutic targets. Targeted therapies directed against mutated genes (e.g., KRAS, BRCA) and immunotherapy agents are areas of active investigation
- **Neoadjuvant Approaches:** The role of neoadjuvant chemotherapy or chemoradiotherapy in down staging borderline resectable tumors and increasing the likelihood of achieving complete surgical resection is actively studied
- **Advances in Imaging:** Innovations in imaging techniques, including functional MRI and positron emission tomography (PET) scans, aim to improve the accuracy of staging and early detection of recurrence

Supportive Care Innovations: Advances in supportive care, including the use of novel pain management techniques (e.g., EUS-guided celiac plexus neurolysis) and minimally invasive palliative interventions (e.g., EUS-guided gastroenterostomy), are enhancing symptom control and quality of life for patients with advanced disease

Scanned with CamScanner

APPROACH TO DECREASED URINE OUTPUT (Due to CKD)

P/C

Decreased urine output 2 weeks

HOPI (ODPARA)

patient is known case of diabetes and hypertension, presented with ↓urine output for the last 14 days .According to his statement he used to go to washroom 3-4 times a day and 2-3 times at night ,however ,he is now going 1-2 times in a day and sometime just once at night for the last 2 weeks .Additionally , his urine output is also decreased significantly and as per his statement it is hardly 2 glasses of water in 24 hours, however , colour of the urine is normal .initially , his urine output was improved by taking some pills at the morning but for the last 5 days it is not improving even with those medication and it has no exacerbating factors .according to the patient reduced urine output is associated with periorbital swelling that is followed by bilateral swelling of feet's upto ankle joints for last one week and it is pitting in nature .However patient denied …

Now exclude DDs of ↓ urine output (AKI/CKD)

1) Pre-renal causes

- patient denied HX of excessive episode of vomiting
- Patient denied recent HX of loose motions, blood loss, trauma and HX of major surgeries. S
- patient denied HX of distended neck veins , yellowish discoloration of sclera (**Right heart failure**) and shortness of breath on exertion and lying flat (**LVF**)
- patient denied HX of prolong use of medication that increases urine output and HX of previous ultrasound that showed ↓ size of one kidney (**Renal artery stenosis**)
- there is no HX of abdominal distension , black tarry stools and blood in vomiting followed by decreased urine output (**Heptorenal syndrome**)

2) Renal causes

- patient denied any HX of blood in the urine or frothy urine (**GN**)
- patients denied any HX of recent respiratory /skin infection followed by decreased urine output , blood in urine and body swelling (**PSGN**)
- there is no HX of chronic HBV&HCV infection ,(tattooing, piercing and surgery) IV drug abuse , high risk sexual behaviour (HIV) (**GN**)
- there is no HX of chronic use of analgesic medication or HX of contrast media , GOLD, penicillin or Hakeem medication(**Drug Induced Nephropathy**)
- there is no HX of oral ulcer , skin rash , joint pain or deformity and Hairloss (**Autoimmune /Vasculitis**)
- there is no HX of ↑ intake of red meat ,recurrent painful swelling of big toe or previous HX of ↑uric acid in the body (**Gout nephropathy**)
- there is no HX of bone fracture on trivial trauma , back pain , constipation and pallor of complexion (**multiple myeloma**)
- there is no Family HX of deafness , visual problems and past HX of renal transplant (**Alport syndrome**)

Scanned with CamScanner

- There is no family HX of renal problem associated with stroke or HX of flank fullness ,recurrent urinary tract infection and valvular problem **(APCKD)**
- there is no HX of bloody diarrhoea , headache and altered sensorium associated with decreased urine output **(HUS/TTP)**
- there is no HX of fever , flank pain and burning micturition **(pyelonephritis)** or HX of recurrent urinary tract infection and HX of small size kidneys on ultrasound **(Chronic Pyelonephritis)**
- there is no HX of recent renal transplant that is followed by ↓urine output **(Acute rejection of transplant)**

3) Post-Renal Causes)

- there is no HX of renal stones , past/family HX of renal & genitourinary malignancy or radiation exposure (radiation etc for retroperitoneal fibrosis)
- there is no HX of instrumentation or procedures of genitourinary tract **(Strictures)**
- There is no HX of difficulty in urination, poor urine stream and dribbling of urine **(BPH & neurogenic bladder).**

Scanned with CamScanner

APPROACH TO PEDAL OEDEM (Due to CKD)

My Patient who is known case of bilateral nephrolithiasis presented with ankle swelling that is gradual in onset, one week in duration and progressive in nature involving both feet followed by bilateral thigh, and finally abdominal wall. there is formation of a pit or/ depression on pressing the feet .this swelling is exacerbated by prolong standing and walking while it is decreased by placing pillow under feet .initially it was relived with diuretics but now it is unresponsive to treatment . Patient experiences heaviness in limbs leads to difficulty in walking; however, there is no Hx of overlying skin changes like redness, itching or pain. This swelling is associated with periorbital puffiness, decreased urine output and shortness of breath on mild to moderate exertion , however , there is no SOB on lying flat and disturbed night sleep that improve on prop-up position.. However there is no HX of

Now exclude few important DDs of ankle swelling

- There is no HX of SOB on lying flat and disturbed night sleep (**heart Failure**
- No Hx of distended neck vein, contact or past HX of TB (**constrictive pericarditis**
- There is no Hx of chronic lung pathology (like COPD and ILD) associated with these symptoms (**Cor-Pulmonale)**
- There is no Hx of decreased intake of protein diet and chronic diarrhoea(**Hypoalbuminemia)**
- There is no Hx of chronic hepatitis B&C infection, black tarry stool and blood in vomiting (**Chronic Liver Disease**
- There is no Hx of oral ulcers, photosensitivity, hair fall, arthralgia or arthritis, (palpable) petechial skin rash and blood in sputum or urine plus constitutional symptoms(**Autoimmune Disorder**)
- There is no Hx of moon face, easy brusibility, new onset diabetes and hypertension (**Cushing syndrome**
- there is no Hx of prolong intake of medicine like NSAID, CCB, steroid and anti-diabetic like pioglitazone (**Drugs induced pedal oedema)**
- There is no HX of pelvic radiation, surgery and trauma (**Lymphedema**)
- No Hx of weight loss, lumps& bumps, and decreased appetite (**Malignancy)**
- However, There is Hx of decrease urine output that is frothy (**CKD Local causes**
- Patient denied HX of recent surgery , immobilization and blood thinning medication (**B/L DVT)**
- There is no HX of fever, redness& painful overlying skin and restriction of movement(**Cellulitis**)
- **remember 6Cs for all sort of body swelling**

1) CCF
2) CKD
3) CLD
4) Cor-Pulmonale
5) Cancer
6) Chronic diarrhoea

Scanned with CamScanner

APPROACH TO VOMITING (Due to CKD)

Patient who is known case of diabetes for the last 15 years and hypertension for the last 10 years, presented with complaint of vomiting for the last 5 days that was of sudden in onset ,episodic ,progressive and non-projectile in nature .initially, patients experienced 4-5 episodes /day containing undigested food particles without clotted or fresh blood and quantified by patients as full cup of tea and it has no specific timing .However, for the last 3 days, patient has persistent vomiting and is unable to tolerate even a single sip of water and that were not relived with multiple intravenous antiemetic injections .it was exacerbated with intake of food and water , however ,there was no reliving factors . Vomiting was associated with either **SOB, /or decreased urine output** and or /**generalized body swelling** (elaborate the associated symptoms).However, there is no HX of ....

Now excluded few imp DDs of vomiting

1) Acute infection

i) CNS (meningoencephalitis /SOL) → there is no HX of photophobia, early morning headache, irritability and altered behaviour

II) ENT→ there is no HX of discharge of pus or ringing sound in ear or sore throat and HX of cough with rusty sputum production

III) Genitourinary→ There is no HX of burning micturition, flank pain and fever.

2) Inflammation

i) GERD →there is no HX of retrosternal burning and regurgitation of food

ii) PUD→ there is no HX of epigastric burning sensation that improves or worsens with food intake.

iii) Pancreatitis →there is no HX of severe epigastric pain that is radiating to back precipitated by gall stones or alcoholism

iv) Hepatitis →there is no HX of yellow discoloration of sclera and painful right hypochondrium

vi) Inflammatory Bowel Diseases→ There is no HX of oral ulcer, any mass or heaviness in RIF associated with bloody diarrhoea.

3) Malignancy (esp. GI related) → there is no HX of ↓appetite, lumps & bumps in the body, difficulty in swallowing and blood in the stool.

4) Motion sickness →there is no HX of recent travel associated with vertigo, tinnitus and vomiting.

5) Autoimmune like SS/SLE→ there is no HX of skin tightness, oral ulcers, skin rash and painful joints.

6) Endocrine causes

A) DKA →patient denied recent HX of polyuria, polydipsia associated with abdominal pain and vomiting

B) →Hyperthyroidism there is no HX of heat intolerance, tremors and palpitation

C) Addison disease→ patient denied HX of dizziness from standing on sitting position and darkening of complexion

Scanned with CamScanner

D) Hyperparathyroidism→ there is no HX of constipation, bones pain, flank pain and psychiatric problems

7) MI →there is no HX of diabetes, lipid disorder and left sided chest pain that radiate to jaw

8) Pregnancy →there is no HX of recent gestational amenorrhea

9) Drugs →there is no HX of alcoholism, chemotherapy agents, antibiotics and organophosphate

10) CKD →long case here

11) Psychological (like bulimia nervosa) →there is no HX of poor eating followed by induced vomiting

Scanned with CamScanner

APPROACH TO BLOOD IN URINE (Due to CKD)

See ITP in Haematology section.

APPROACH TO ALTERED SENSORIUM (Due to CKD)

See neurology section for approach to altered sensorium.

CARE/RECA

As we have discussed the causes /risk factors for CKD/AKI (esp. those associated with decreased urine output) but in most cases CKD is due to DM, HTN and renal stones etc and (therefore you should only exclude relevant causes/risk factors instead of wasting time for excluding each and every risk factors/causes of CKD)

Ask about Complication of CKD like

Haematological complications

- Anemia
- Coagulopathy

Neurological complications

- Uremic encepalotahy
- Peripheral neuropathy
- Autonomic dysfunction like erectile dysfunction
- Restless leg syndrome

(The last 3 complication may not improve with dialysis)

Endocrinology complication

- Erectile dysfunction in men due to low testosterone
- Women are often anovulatory

Electrolyte imbalance

- Arrhythmias due to hyperkalaemia

Metabolic Bone Disease

- Like hyperphosphatemia, hypocalcaemia and low vitamin D
- Adynamic bone disease
- Proximal myopathy
- Osteomalacia

Cardiovascular Complications

- Hypertension (the most common complication of CKD)
- Coronary artery disease/IHD
- Heart Failure
- pericarditis

Now

Ask relevant **ITP** (investigations, treatment and procedures) &

PAM-HUGS-FOSS-TV-F

Examination:

Always look for AV-fistula and catheter mark

Vitals

Scanned with CamScanner

GPE → half and half nail, Leukonychia, pin-prick marks (DM), asterixis, uremic frost, scratch marks, bruising, AV fistula, JVP, CVP line, anemia, jaundice, periorbital puffiness, hyperventilation and fetor

Systemic examination

Abdomen →scar mark for peritoneal dialysis, flank fullness and palpable kidneys (due to APCKD and hydronephrosis and other causes) renal tenderness (pyelonephritis) and tenderness over the transplant kidney (failing transplant) evidence of ascites (due to dialysis or fluid overload) and renal bruit (due to RAS)

CVS → evidence of heart failure and pericardial rub (due to uraemia)

RESP → pleural effusion and pulmonary congestion

MSK → muscles wasting, bones tenderness and proximal myopathy

Neurology → mental status and peripheral neuropathy

Examinations of fistula → to check the weather it is functional or non-functional

Scanned with CamScanner

VIVA of CKD

When you label a patient as CKD?

When there is kidney damage or abnormal GFR (<60mL/min /1.73m^2) for ≥ 3 months (while the Kidney damage is defined as pathologic abnormalities or marker of damage, including abnormalities in blood or urine tests or imaging studies)

How will you investigate CKD patient?

- **CBC** →Anemia
- **RFTs**→ to assess progression compare to previous result
- **Urine R/E**→ for quantification of proteinuria and may also show haematuria and caste
- **Electrolyte** → Hyperkalaemia
- **Renal ultrasound** → may show shrunken kidneys & loss of CM junction ,renal stones ,polycystic kidneys and asymmetrical renal size
- **PTH, Ca, PO4 & vit D** → may reveal metabolic bone disorder like secondary hyperparathyroidism
- **CXR** → may shows effusion
- **ECG** → may shows IHD & pericarditis
- **Lipid profile ,HBA1c**
- **HBV &HCV serology**
- **Renal Scan like DTPA &DMSA** →for assessment of structure of kidneys and GFR calculation

Causes of anuria (<100 mL/ day)	
Condition	Examples
Urinary obstruction (complete)	• Urinary retention due to prostatic enlargement, urethral stenosis, bladder tumour • Bilateral ureteric obstruction due to retroperitoneal fibrosis, cancer, radiation injury • Bilateral renal stones (mostly by staghorn calculi) • Massive crystalluria induced obstruction of tubules
Lack of renal perfusion (bilateral)	• Aortic dissection involving renal arteries Severe acute tubular necrosis • Severe functional hypoperfusion (cardiorenal, hepatorenal)
Rapidly progressive glomerulonephritis	• Anti-glomerular basement membrane disease, severe antineutrophil cytoplasmic antibody (ANCA) vasculitis (100% glomerular crescents on biopsy)

What are causes of anaemia in CKD?

- Deficiency of erythropoietin
- Reduced red cell survival
- Toxic effects of uraemia on bone marrow

Scanned with CamScanner

- Blood loss due to fragility of capillaries and coagulopathy
- Reduced intake , absorption and utility of iron
- Blood loss during procedures like CVP and fistulas etc

Causes of glomerulonephritis associated with low serum complement

- Post-infectious glomerulonephritis(LowC3)
- Subacute bacterial infection, especially endocarditis (Low C3&C4)
- Systemic lupus erythematosus(LowC3&C4)
- Cryoglobulinaemia (Low C3&4)
- Mesangiocapillary glomerulonephritis(low 3)

What are the causes of CKD with palpable kidneys?

- APCKD
- B/L hydronephrosis due to any cause
- Diabetic nephropathy
- Systemic sclerosis
- Amyloidosis
- Multiple myeloma
- HIV associated nephropathy (HIVAN)
- Acute renal vein thrombosis

Common causes of CKD worldwide

- DM, HTN and Chronic GN while the last one is also the most common cause of CKD in developing countries.

What are the stages of CKD?

Stage	Definition	Clinical presentation
1	Kidney damage with normal or high GFR (>90)	Asymptomatic
2	GFR 60-89	Patient are Asymptomatic
3A	GFR 45-59	Usually asymptomatic
3B	GFR 30-44	Anaemia in some patients at 3B
4	GFR 15-29	Electrolyte problems likely as GFR falls
5	GFR <15 or on dialysis	Significant symptoms and complications usually present Dialysis initiation varies but usually at GFR <10

Scanned with CamScanner

How will you mange complications of CKD?

Treat the underlying cause and complications are the mainstay of management of CKD.

1) Proteinuria

Patients with proteinuria are at higher risk of progression of renal disease and therefore reducing proteinuria reduces the progression. The treatment of proteinuria is ACEs/ARBs as it reduces BP as well as glomerular perfusion pressure and ACES have also been shown to reduce cardiovascular events and all-cause mortality in CKD. They may reduce GFR due to its mode of action and therefore patient should check their renal function checked within7-10 days of initiation or dose increment and it is recommended to stop it when temporarily when patient is unwell and when there is acute on chronic CKD. Additionally, the most likely therapy to reduce proteinuria after ACES/ARBs **is spironolactone**

Quantifying proteinuria in random urine samples

ACR	PCR	Dipstick results	Importance
<3.5 female) <2.5 male)	<25	-	Normal
3.5-30	25-50	-	Moderately elevated albuminuria
30-70	50-100	+ to ++	Dipstick positive
70-300	100-350	++ to +++	Glomerular disease is more likely; equivalent to 1 g/24 hrs
>300	> 350	+++ to ++++	Nephrotic range: almost always glomerular disease, equivalent to > 3.5 g/24 hrs

2) Dyslipidaemia

Statin is indicated with dose adjustment when there is deranged lipids profile

3) Heart failure it may be multifactorial like due to HTN, fluid overload, anaemia and atherosclerosis (again, it is due to many factors). Treatment is same like general population. SGLT2 improves outcomes in heart failure and CKD

3) Pericarditis

Uremic pericarditis may occours in CKD patients and may complicate cardiac tamponade therefore it should be treated promptly with dialysis (with minimal or no heparin).NSAID should be avoided in uremic pericarditis.

4) Metabolic Bone Disease /renal osteodystrophy

This may manifest during **stage 3 CKD** and characterized by low Ca and ↑PO4 and PTH. The most common bone disease is osteitis fibrosa cystica and is due to secondary hyperparathyroidism. Treatment is correction of Ca, PO4 and PTH toward normal and in simple words control of hyperparathyroidism. Therefore CKD patient should avoid dietary phosphorus and followed by oral phosphate binder if needed. Oral phosphate binder include calcium containing binder l(like calcium carbonate 650mg, calcium acetate 667mg(tab Lophos®) one to three tablets /day it is indicated when there is low Ca and high PO4) and non-calcium phosphate binder like sevelamer

Scanned with CamScanner

carbonate 800-3200mg/meal(tab Neosev®)and lanthanum carbonate (500-1000mg/meal) .**There Are Recent Advances** where new agents like iron based phosphorus binder namely **ferric citrate** and **sucroferric oxyhydroxide** are available and indicated when older agents cant not be used (due to constipation and Hypercalcemia) .

Once phosphate level become normal it is easy to treat **secondary hyperparathyroidism** by active vit D 500IU/day (0.25-0.5 mcg/day) and **Cinacalcet** (in case there is ↑Ca&PO4, and vit D can't be used) 30-90mg orally/day (target calcium-sensing receptors and ultimately supress the PTH production).Due to skeletal resistance to PTH with uraemia, relatively high level are targeted in advanced CKD to avoid Adynamic bone disease. it is recommended that PTH level should be keep near or just above the upper limit of normal for moderate CKD and 2-9 times the upper limit of normal in ESKD.

Component of renal osteodystrophy are, osteomalacia, osteoporosis, osteoseclerosis and hyperparathyriod bone disease like osteitis fibrosa cystica.

5) Anemia

Anemia in CKD may be due to many factors and the most commonly due to reduced production of erythropoietin .Anemia becomes clinically significant in stage 3 CKD and the firs line investigation for Anemia in CKD is Haematinics (B12, folic acid, ferritin & iron saturation).In CKD patient ,serum ferritin below 100-200ng/mL or iron saturation is less than 20% is suggestive of Anemia and this may be corrected with oral or parenteral iron until serum ferritin level is more than 500-800ng/mL and at this level stop further iron therapy even if iron saturation is less than 20%(functional Anemia) . Oral therapy (ferrous sulphate, gluconate and fumarate 325mg/day) is indicated for CKD patient who is not on dialysis, and when HB is less than 9g/dL and iron stores are adequate, erythropoiesis –stimulating agents like erythropoietin (50-100units/kg once or twice a week) and darbepoetin (0.45mcg/kg every 2-4 weeks) subcutaneously or intravenously and target HB should be 10-11d/dL as higher HB is associated with stroke and other CVS complications.

Targets

HB →10-11g/dL

Ferritin → in pre dialysis and peritoneal dialysis patients > 100 ug/L while haemodialysis it should be > 200 ug/L

Transferrin saturation > 20%

Haematocrit <33% and percentage hypochromic red cells <6%

6) Coagulopathy

Bleeding disorder may occours in stage 4-5 and primarily due platelets dysfunction due to uraemia and to some extent Anemia. Desmopressin (25mcg BD) is an effective treatment for platelets dysfunction and indicated in CKD patients undergoing surgery while conjugated oestrogen (tab Premarin® 0.3mg) is also effective but the best modality for bleeding diathesis is dialysis.

7) Neurological complications

It occours in advanced CKD and primarily treated with dialysis with variable response

Scanned with CamScanner

8) Acid-base imbalance

Due to ↓ excretion of acid resulting in the excess acid in the body that is buffered by leaching of calcium and phosphorus from the bones (resulting in metabolic bone disease).This is managed by restriction of protein and ↑ intake of vegetables & fruits along with sodium bicarbonates administration (0.5-1.0 mEq/kg/day).

9) Hyperkalaemia

Potassium level remain within range until CKD stage 4-5, if there are no other contributing factors like RTA and drugs . Acute hyperkalaemia is medical emergency and should be treated with 10% calcium gluconate (5-30ml intravenously), insulin (5-10 units in 50% dextrose) ,nebulization with beta agonist (salbutamol 5-10mg or albuterol 10-20mg in 4 ml normal saline), $NaHCO_3$ (50-100mEq), K-oxylate(15-30g diluted in syp Duphalac) ,diuretic therapy and if resistant to all measures than dialysis .Chronic hyperkalaemia is treated with dietary restriction(2g/day) . minimize or eliminate the culprit drugs and calcium resonium (↓ gut absorption of potassium) as short-lived measures(long-term use is associated with gut necrosis). However, newer agents such as **zirconium cyclosilicate** and [illegible] can be used for long term treatment of hyperkalaemia.

10) Dietary restrictions

Reduced intake of animal Protein (0.6-0.8g/kg/day) may slow CKD progression while 2g/day sodium, 50-60 mEq/day potassium and 800-1000mg phosphorus intake is recommended for CKD patient and fluid intake should be 2L/day if there is volume overload.

11) Pruritus

Exclude other causes of pruritus and check the quality of dialysis .it can be treated with anti-histamine, moisturizing ointment, activated charcoal, SSRIs and naltrexone etc.

12) Hypertension in CKD

It may be either complication or cause of CKD

According to JNC-8 guidelines BP target in CKD patients should be less than 140/90 while American Heart Association (AHA) recommend less than 130/80 mmHg while NICE guideline recommend target BP of <130/90 for protinuric CKD and less than 140/90 for non-protinuric CKD, less than 110/70 for APCKD and less than 125/75 for IgA nephropathy .while KDIGO recommends a target blood pressure of less than 120/80 mmHg for CKD patients.

What is the criterion for referral of chronic kidney disease patients to a nephrologist?

1. eGFR <30 mL/min/1.73 m²
2. Rapid deterioration in renal function (>25% from previous or >15 mL/min/1.73 m²/year)
3. Significant proteinuria (PCR > 100 mg/mmol or ACR > 70 mg/ mmol), unless known to be due to diabetes and patient is already on appropriate medications
4. ACR >30 mg/mmol with non-visible haematuria
5. Hypertension that remains poorly controlled despite at least four antihypertensive medications
6. Suspicion of renal involvement in multisystem disease

Scanned with CamScanner

How to slow down progression of CKD?

Optimum control of diabetes, HTN, weight loss if overweight, avoids nephrotoxic drugs and addition of SGLT2 inhibitors in patients with or without diabetes may slow down progression of CKD.

CKD in pregnancy

In stage I&II CKD, continue pregnancy and the outcome is normal while if there is rapid rise of creatinine or end-stage disease conception should be avoided. As there are increased risks of complications like eclampsia, HELLP, DIC, acute fatty liver of pregnancy and thrombotic microangipathy .Therefore, patient should be started on low-dose of aspirin from conception till 36 weeks to ↓risk of eclampsia and close monitoring of foetal and mother wellbeing is recommended.

Anticoagulation in CKD

The preferred agent is heparin

Vaccination in CKD

Influenza, Pneumococcal and HBV

Cause of death in CKD

Due to Cardiovascular /IHD

Haemodialysis (HD)

- It is usually carried out for 3-5 hours duration and 3times/week (or 2-3hours for 5-7 times/week) .The duration and frequency of dialysis in CKD patients should be adjusted to achieve a reduction in urea during dialysis of more than 65% as below this level is associated with ↑ mortality .

Peritoneal Dialysis

- It is done by insertion of a permanent silastic catheter into the peritoneal cavity .it is of two types

i) Continuous Ambulatory Peritoneal Dialysis (CAPD)

- In CAPD ,2L of sterile , isotonic dialysis fluid are introduced and left for 4-6 hours and this fluid is then drained and fresh dialysis fluid is introduced in a continuous four –times daily cycle .during all this time , patient is mobile and able to carry out normal daily activities

ii) Automated Peritoneal Dialysis (APD)

- It is similar to CAPD but uses a mechanical device to perform the fluid exchange during the night or with only a single exchange to perform during the day.
- **Renal replacement therapy (RRT)means** the facility to replace functions of the kidney like HD or peritoneal dialysis

Indications of Dialysis

- Uraemia(like encephalopathy , pericarditis and bleeding diathesis)
- Resistant Hyperkalaemia
- Fluid overload
- Metabolic acidosis

Time for maturation of A-V fistula

Scanned with CamScanner

6-8 weeks

Comparison of haemodialysis and peritoneal dialysis

Peritoneal dialysis
1)Less effective ; four exchanges per day are required, each taking 30-60 mins (continuous ambulatory peritoneal dialysis) or 8-10 hrs each night (automated peritoneal dialysis
2)A few hours between treatments
3)May Performed at home
4)Requires an intact peritoneal cavity without major scarring from previous surgery or infections
5)Diet and fluid less restricted
6)Slow continuous fluid removal, usually asymptomatic
7)Peritonitis and catheter-related infections may occur
8)Patients usually non-dependent on others

Haemodialysis
1)More Effective ; 4 hrs three times per week is usually adequate
2)2-3 days between treatments
3)Requires visits to hospital (although home treatment is possible for some patients)
4)Requires adequate venous circulation for vascular access
5)Careful adherence to diet and fluid restrictions required between treatments
6)Fluid removal compressed into treatment periods; may cause symptoms and haemodynamic instability
7)Infections related to vascular access may occur
8) Patients are usually dependent on others

Renal Biopsy

Indications

- AKI/CKD of uncertain aetiology
- Nephritic syndrome
- Nephrotic syndrome or glomerular proteinuria(PCR ratio > 100mg/mol) in adult
- Renal transplant dysfunction

Contraindications

- Uncontrolled hypertension
- Bleeding due to coagulopathy or low platelets
- Single kidney (except transplant)
- Small size kidney (<60 % predicted size)

Complications

- Infection
- Bleeding into ureter causing obstruction and around the kidney that may require surgery or sometime nephrectomy

Scanned with CamScanner

- A-V fistula formation

Renal Biopsy Needle

- **Monopty Gun**

What are the Complications of Haemodialysis?

Complications	Cause	Treatment
During treatments **Hypotension**	Fluid removal and hypovolaemia	Saline infusion; exclude cardiac ischemia
Cardiac arrhythmias	Potassium and acid-base shifts	Check K+ and arterial blood gases: review dialysis prescription; stop dialysis
Haemorrhage	Anticoagulation Venous needle disconnection	Stop dialysis and consider heparin-free treatment
Air embolism	Disconnected or faulty lines and equipment malfunction	Stop dialysis
Dialyser hypersensitivity	Allergic reaction to dialysis membrane or sterilisant	Stop dialysis; change to different artificial kidney
Between treatments **Pulmonary oedema**	Fluid overload	Ultrafiltration + dialysis
Systemic sepsis	Usually involves vascular access devices (catheter or fistula)	Blood cultures; antibiotics

Complications of continuous ambulatory peritoneal dialysis

Complications	Cause	Treatment
Peritonitis	Usually entry of skin contaminants via catheter; bowel organisms less common	Culture of peritoneal dialysis fluid Intraperitoneal antibiotics, tobramycin, vancomycin Catheter removal sometimes required
Catheter exit site infection	Usually skin organisms	Antibiotics; sometimes surgical drainage
Ultrafiltration failure	Damage to peritoneal membrane, leading to rapid transport of glucose and loss of osmotic gradient	Replacement of glucose with synthetic, poorly absorbed polymers for some exchanges (icodextrin)
Peritoneal membrane failure	Scarring/damage to peritoneal membrane	Increase in exchange volumes; consideration of automated peritoneal dialysis or switch to haemodialysis
Sclerosing peritonitis	Unknown; typically occurs after many years	Switch to haemodialysis (may still progress) Surgery and tamoxifen may be used

Scanned with CamScanner

Renal Transplant

Renal transplant is the most cost effective treatment and offer best chance of survival in ESRD patient's .During the procedure, the recipient kidney is not removed (may be removed pre-transplant if it is the source of repeated sepsis or in case of APCKD) but the donor kidney is placed in the pelvis and vessels are anastomosed with recipient external iliac artery and vein and donor ureter to the recipient bladder .post-transplant patient survival from cadaver donors is 96% at 1 year and 88% at 5 years. Contraindications of transplant includes active malignancy, vasculitis, high risk of recurrence (MCGN >IgA>FSGS) and low life expectancy while HIV is not contraindication of transplant until CD4 counts are less than 200 for more than 6 months . Complications include infections and malignancy due to immunocompromised state. Cost of transplant 25-30 lac approximately .HLA, ABO grouping and exclusion of active CMV infection is advised before transplant.

What is cardiorenal syndrome?

It may be defined as any acute or chronic problems in heart or kidney that could result in an acute or chronic problem of the other.

Type I →Acute HF leading to AKI
Type II→ chronic heart failure leading to CKD
Type III→ AKI leading to HF (Acute renocardiac)
Type IV →CKD leading to heart failure (Chronic renocardiac)
Type V →HF&CKD secondary to systemic cause (secondary renocardiac)

Indication of parathyriodectomy

- When hyperparathyroidism is not responding to medical therapy (resistant)
- Tertiary hyperparathyroidism
- Severe pruritus

Recent advances in CKD

Finerenone (10 ,20mg)→ (a non-steroidal selective mineralocorticoid receptors antagonist) is indicated to reduce the risk of sustain decline of GFR , cardiovascular death , non-fatal myocardial infarction and hospitalization for heart failure in adult with chronic kidney disease associated type 2 diabetes mellitus . In simple words, it offers cardiorenal protection. Carbamyoglban (Fibroblast Growth Factors 23) Fibroblast Growth Factors 23 are extremely elevated in CKD patients and associated with ↑ mortality and an independent predictor of mortality in *CKD.

Scanned with CamScanner

Prognosis

Patient on dialysis have average life expectancy of 3-5 years but survival upto 25 years may be achieved depending on the cause and comorbids. CKD due to diabetes and GN are associated with poor prognosis.

Criteria for acute kidney injury

What is KDIGO/RIFLE criterion for AKI?

KDIGO (Kidney disease: Improving global outcomes)	**RIFLE Criteria** (Risk Injury Failure, Loss,End Stage)
Stage 1: serum creatinine increase >1.5-1 -fold, urine production of<0.5 mL/kg/hr for 6-12 hrs	=Risk
Stage 2: serum creatinine increase >2.0-2.9 -fold, urine production of <0.5 mL/kg/hr for ≥12 hrs	= Injury
Stage 3: serum creatinine increase > 3.0-fold, urine production of < 0.3 mL/kg/hr for ≥ 24 hrs or absolute anuria for ≥ 12 hrs, or absolute serum creatinine > 354 µmol/L with an acute rise >44 µmol/L	= Failure
End-stage renal disease: need for renal replacement therapy for 3 months	Loss: persistent AKI, or complete loss of kidney function for >4 wks.

Management of AKI

- Assess fluid status as this will determine fluid prescription:
  - If hypovolaemia: optimise systemic haemodynamic status with fluid challenge and inotropic drugs if necessary
  - Once euvolaemic, match fluid intake to urine output plus an additional 500 mL to cover insensible losses
  - If fluid-overloaded, prescribe diuretics (loop diuretics at ↑doses may be required); if the response is unsatisfactory, dialysis may be indicated
- Administer calcium resonium to stabilise myocardium and glucose and insulin to correct hyperkalaemia if K+ >6.5 mmol/L as a temporary measure until a definitive method of removing potassium is achieved like dialysis or restoration of renal function
- Consider administering sodium bicarbonate (100 mmol) to correct acidosis if pH<7.0)
- Discontinue potentially nephrotoxic drugs and reduce doses of
  - therapeutic drugs according to level of renal function
- Ensure adequate nutritional support
- Consider proton pump inhibitors to reduce the risk of upper gastrointestinal bleeding
- Screen for intercurrent infections and treat promptly if present
- In case of urinary tract obstruction, drain lower or upper urinary tract as necessary

Scanned with CamScanner

APPROACH TO POLYURIA (Due to DM)

P/C Excessive Urination /Urine Output …….. 2 months

HOPI (ODPARAV)

My patient presented with complaint of excessive urination for the last 2 months, that is sudden in onset progressive in nature as initially he experienced 3-4 episodes in day and 2-3 episodes at night but for the last 20 days he has to go 6-8 times a day and 3-4 times at night for urination while the volume of urine is normal and there is no discoloration of the urine .it has no exacerbating factor and does not improve even if patient drinks less amount of water. It is associated with increased thirst, increased appetite, body aches and tingling & numbness in the feet's. However, there is no HX of….

Now exclude few imp DDs of polyuria

1. **DM** (long case here)
2. **Diabetes insipidus(Cranial /nephrogenic)** →patient denied any HX of trauma to the head or recent HX of head surgery and HX of mood disorder (**Lithium induced nephrogenic Diabetes insipidus)**
3. **Hypercalcemia (due to any cause)**→patient denied HX of constipation , epigastric pain , low mood and flank pain
4. **Sarcoidosis** →patient denied HX of dry cough and painful skin nodule
5. **Renal disorder(polyuric phase)** →patient denied any HX of ingestion of nephrotoxic drug /HX of blood loss and acute gastroenteritis that caused ↓ urine output followed by excessive micturition
6. **Drugs** →there is no HX of chronic alcohol intake and HX of medication like diuretics
7. **Psychogenic polydipsia** →patient denied HX of mood swings when he takes large amount of water

Scanned with CamScanner

APPROACH TO NUMBNESS OF HANDS & FEET (Due to DM)

P/C **Numbness of Feet .....2 months**

Patient presented with complaint of numbness in feet for the last 2 months that is gradual in onset and 2 months in duration .According to the patient he describes numbness as inability to feel sensation in both feet upto ankle joints that equally involved the feet bilaterally symmetrical while rest of the body the sensation is intact .it is continuous and has no exacerbating & reliving factors and it is associated with increased intake of water, foods and body aches, but patient denied any burning & tingling sensation in the body. However, there is no HX of .....

(Ask what does patient mean by numbness either lack of sensation or abnormal sensation in body)

Now exclude imp DDs of numbness /paresthesia

1. **DM →long case here**
2. **CKD** →patient denied HX of deceased urine out , sallow complexion and frothy urine
3. **Pernious Anemia(B12)**→ patient denied HX of pallor of complexion , inability to maintain balance in night and white patch(vitiligo) on skin
4. **Autoimmune Disorder(vasculitis)** →patient denied HX of joints pain , palpable skin rash and hair loss
5. **HIV** →patient denied HX of high risk sexual behaviours and IV drug abuse
6. **Leprosy /Lyme disease** →patient denied an expanding skin rash, thickenings of the nerves and depigmented skin patches.
7. **CNS causes (MS, stroke , migraine etc)** →patient denied HX of transient visual loss followed by spontaneous improvement and HX of difficulty in speaking , loss of power in any part of the body and HX of uncontrolled movements of body with or without loss of consciousness(epilepsy)
8. **Paraeneospalstic(due to malignancy)** →there is no HX of weight loss , lumps& bumps in the body and decreased appetite
9. **Drugs induced numbness** →patient denied taking drug like ATT(isoniazid), anticancer drugs (vincristine & cisplatin) and antiepileptic drug like phenytoin
10. **CIDP** →patient denied HX of weakness in lower limbs that wax and wanes over period of time
11. **Hypoparathyroidism** →patient denied HX of neck surgery , twitching of muscles and bones pain

Scanned with CamScanner

APPROACH TO FOOT ULCER (Due to DM)

P/C **Wound on Foot -----1 month**

HOPI (ODPARAV)

Patient presented with wound on the dorsum of right foot (or on base of the big toe) that is gradual in onset, 1 month in duration .According to the patient, he initially experienced itching in the affected area that is followed by blister formation and ultimately convert into an ulcer that is 2-3 finger in width, with oozing of serosanguinous discharge followed by pus formation and redness of the surrounding area. The wound is painless and foul smelling .it has no exacerbating & reliving factors .it is associated with numbness in the feet ,body aches, excessive intake of water and foods .the patient took some medication from local doctors but it was not responding rather worsening day by day .However , there is no HX of .....

Now exclude imp DDs of foot ulcer

1. **DM**
2. **Trauma** → there is no HX of any sort of recent trauma
3. **Insect bite** →there is no HX of insect bite
4. **Venous ulcer due to varicose vein** →there is no HX of engorged tortuous vein in the affected limb
5. **Arterial ulcer** →there is no HX of lipid disorder and pain in calves on walking or HX of SOB and left sided chest pain on exertion
6. **Neuropathic ulcer** → there **is HX of abnormal sensation** the feet upto ankle joint associated with burning sensation at night time
7. **Infection (like TB , leprosy and Leishmaniasis)** →there is no HX of contact with TB patient , recent tics bite and depigmented white patch on skin
8. **Haematological (sickle cell , PNH etc)** → there is no HX of severe pain in bones , recurrent chest pain and early morning red discoloration of urine
9. **Neoplastic (SCC, BCC and malignant melanoma)** →there is no HX of excessive sun exposure etc
10. **Vasculitis (burger , PAN and Cryoglobulenemia)** → there is no HX of palpable skin rash , joint pain and alteration of colour of toes in winter associated with Smoking

Scanned with CamScanner

APPROACH TO UNCONTROLLED BLOOD SUGAR

This is a common presentation of diabetic patient and you are supposed to ask questions to determine the cause, like compliance with diabetic medicine & dietary restriction, recent intake of khakeemi medicine, infection, stress, affordability issues, weight gain, corticosteroid use (cushingiods), and change in the body habitus (acromegaly).

CARE of Diabetes

- **Diet & obesity** → my patient is overweight, has sedentary life style and in habit of overeating
- **Pancreatic problems**→ there is no HX of recurrent abdominal pain radiating to back (on background of alcohol excess intake or gall stones or fibrocalculous pancreatic diabetes)
- **Cushing syndrome** →there is no HX of easy brusibility of skin ,abdominal distension and drumstick appearance of the limbs
- **Khakeemi medication / steroid use → there is no HX of khakeemi medication or intake of steroids**(gandam ki tarah choti golian jo supad ya kaligi rang kai hu)
- **Acromegaly** →there is no HX of ↓ vision , increased size of the shoes and spade like hands
- **Hemochromatosis**→ there is no HX of joints pain, difficulty to maintain erection and gray to brown discoloration of sun-exposed skin.
- **Gestational diabetes**→ there is no HX of polyuria ,polydipsia in previous or current pregnancy
- **Primary diabetes**→ he /she has many siblings suffers from diabetes.
- Ask about **other autoimmune disorders** like there is no HX of heat/cold intolerance & enlarged mass in front of neck , dizziness on standing from sitting position(Addison) ,vitiligo and pallor of complexion (Pernious Anemia)
- **Ask Complication of Diabetes**
- **Retinopathy** →there is no HX of ↓ visual acuity or feeling of curtain over the **eyes**
- **Diabetic nephropathy**→ there is no HX of frothy urine& periorbital swelling
- **Diabetic neuropathy** →there is no HX of numbness ,burning & tingling sensation in hands & feet and weakness in any part of the body
- **Autonomic neuropathy** →there is no HX of early satiety , dizziness on standing from sitting position, erectile dysfunction , sweating and racing of heart on rest
- **Diabetic foot diseases** →there is no HX of ulcer formation in feet or painless swelling and redness of joint of foot (Charcot arthropathy)
- **Macro vascular complications**→ there is no HX of previous MI / or stroke and pain in chest and legs on exertion
- **Proximal myopathy**→there is no HX of difficulty standing from sitting position
- **Frozen shoulder** →there is no HX of restriction of movements of at shoulder joint
- **DKA/HONK**→ There is no HX of altered sensorium ,shortness of breath associated
- **Hypoglycaemia and the its cause** →there is no HX of double vision, tremors and difficulty in speaking associated with low blood sugar (ask why it happened, did you miss the meal , over dose of insulin or any problem with liver or renal system)
- **Poor wound healing**
- **Complications of antidiabteic drugs** → weight gain , GI disturbance and hypoglycaemia etc
- **ITP** (investigations, treatment and procedures)

Scanned with CamScanner

Now ask relevant

- **PAM-HUGS-FOSS-TV-F while in medicine/Drug HX , you are expected to ask certain question regarding insulin**

1. Type of insulin(water like(regular insulin) or milk like (NPH insulin or mixtard due to NPH)
2. Site of injection (ask atrophy or hypertrophy of fats and due you change the site)
3. How many units in morning and evening , any additional units(frequency)
4. Who inject insulin and patient understanding of units and can they see units on syringe clearly or have visual problems
5. Do you check expiry date of insulin
6. Do you have refrigerators in home
7. Do you change insulin syringe after 2-3 times
8. Any episode of hypoglycaemia and how it was manage and patient understanding of hypoglycaemia
9. Who bears the expenses of insulin or treatment and complications (can also be ask in socioeconomic segment of HX)

- **Socioeconomic HX is imp** in diabetes like in other chronic disorders and you are expected to inquire how patient manage all the expenses of treatment and home expenditures

Examination scheme

Vitals

GPE → Onycholysis, fungal infection of digital spaces, fingers pricks, acanthosis nigricans, JVP, oral thrush, facial asymmetry, mucormycosis, cataract, and thyroid

CVS → standard examination including all pulses like radial, carotid and femoral

Resp→

Abdomen → insulin injections marks, hepatomegaly (hemochromatosis and MODI-5), palpable kidneys)

CNS→ examine motor, sensory, reflexes, cranial nerves, autonomic, proprioception, monofilament test, pain and temperature of lower limbs .additionally also look for hair loss and ulcers in the feet

MSK → proximal myopathy and arthropathy,

Fundascopy→

Scanned with CamScanner

VIVA OF DIABETES

- **Define Diabetes**
  It is a chronic endocrine disorder, which is characterized by increased blood sugar level either due to decreased insulin production/secretion or due to increased peripheral insulin resistance.
- **What is the incidence of Diabetes?**
  Type I→5-10%
  Type II→90-95%

- **What are the types of Diabetes?**
- **Type I**
- **Type II**
- **Other Specific Type like** LADA, MODY, Gestational DM, DIDMOAD. Causes of secondary diabetes are drug induced (steroid , thiazide ,phenytoin) , due to hemochromatosis, acromegaly , chronic pancreatitis, cystic fibrosis and associated with certain condition like Fredric's ataxia , turner syndrome and myotonic dystrophy

➢ **Maturity –Onset Diabetes of the Young (MODY) (Type 1.5DM)**

It is characterized by development of type 2 DM in patients less than 25-year old .it is autosomal dominant condition with strong family HX. Sulphonylurea is the initial drugs of choice, because at least for the first few years, these patients have the capacity insulin and use of Sulphonylurea restores the insulin release and therefore avoiding the need for insulin therapy

MODY 1

<10%

Due to defect in HNF-4 alpha gene (Hepatocyte nuclear factor)

MODY 2

20% of cases

Due to a defect in the glucokinase gene

90% of MODY 2 are controlled on diet therapy alone

MODY 3

60% of cases (most common)

Due to a defect in the HNF -1 alpha gene

MODY 4(PDX1) very rare

MODY 5(HNF-1beta) very rare and associated with hepatosplenomegaly

MODY 6(neuroD1) very rare

➢ **Latent Autoimmune Diabetes In Adult (LADA)**

It is type 1 Diabetes that starts in adult and slowly gets worse with time. Symptoms start usually in people who have LADA when they are over 30. At first LADA may be managed with lifestyle changes like exercise regularly, weight loss, stop smoking and healthy diet choice and oral antidiabteic may also be effective but most patients eventually need insulin

Scanned with CamScanner

- **What are the staging of type 1 Diabetes**

1. Only positive antibodies while other labs(RBS) are normal
2. Positive antibodies and Pre-Diabetes e.g. impaired sugar level
3. Positive antibodies and Frank diabetes(symptomatic)

- **What are the antibodies found in newly diagnosed type 1 Diabetes**

1. Islet cell antibodies (ICA)
2. Glutamic acid decarboxylase(GAD65)
3. Anti-insulin antibody
4. Zinc transporter
5. Tyrosine phosphatase

- **What is the risk of type 1 diabetes among first-degree relatives of patients with type 1 diabetes**

Relative with type 1 diabetes	overall risk
Identical Twin→	30-50%
Non Identical Twin→	6-10%
HLA-Identical Sibling→	16%
Non-HLA-Identical Sibling→	5%
Father→	10%
Mother→	1-4%
Both Parents→	30%

➢ **What is the diagnostic criterion of Diabetes?**

- Diabetes is confirmed by either plasma glucose in random sample or 2 hrs after a 75 g glucose load **≥11.1 mmol/L (200 mg/dL)** or
- fasting plasma glucose **≥7.0 mmol/L (126 mg/dL)** or
- HbA_{1c} ≥ 48 mmol/mol(**≥6.5)**

In asymptomatic patients, two diagnostic tests are required to confirm diabetes; the second test should be the same as the first test to avoid confusion

While Pre-Diabetes is defined as

- Impaired fasting glucose → fasting plasma glucose **≥6.1 mmol/L (110 mg/dL) and <7.0 mmol/L (126 mg/dL)**
- Impaired glucose tolerance →fasting plasma **glucose <7.0 mmol/L (126 mg/dL) and 2-hr glucose after 75 g oral glucose drink 7.8-11.1 mmol/L** (140-200 mg/dL)

(NICE guidelines recommend considering an HbA1c range of 42-47 mmol/mol to be indicative of pre-diabetes while the American Diabetes Association (ADA) guidelines suggest a range of 39-47 mmol/mol(HbA_{1c}5.7-6.4).The ADA also suggests a lower fasting plasma glucose limit of ≥ 5.6 mmol/L (100 mg/dL) for Impaired fasting glucose)

➢ **What is the criteria for screening diabetes or pre-diabetes in asymptomatic?**

1. Age ≥ 35-year
2. All first degree relative of type 1 diabetic

Scanned with CamScanner

3. Pre-Diabetes 1 yearly
4. Gestational Diabetes 3 yearly
5. High risk individuals like HTN , PCOS , lipid disorders
6. HIV patients
7. BMI ≥ Asian or ≥ 25-year and there are risk factors

➢ **What is the diagnostic criterion of Gestational Diabetes (GDM)?**

All mothers who have family HX (1st degreee relative) of diabetes, or having other risk factors like diabetes in previous pregnancy, macrosomic baby, HX of polyhydramnios should be screen for gestational diabetes. All women at risk should have an oral glucose tolerance test at 24-28 weeks and if fasting FBS is **>92 mg/dl**(5.1-6.9 mmol/L) and hr blood level **> 180 mg/dL** (>10mmo/L)and 2 hrs **> 153 mg**/dL (>8.5 mmol/L) **after 75 mg OGTT** is diagnostic of gestational diabetes and it is called **one –step strategy** and **two step strategy** is recommended by American College of Obstetricians and Gynaecologists (ACOG) in the two-step approach , non-fasting mother ingest a 50-g oral glucose load , followed by a 1-hour glucose measurement if the 1-hour glucose level is ≥ 200 mg/dL , a diagnosis of GDM is made and no further testing is needed , However , if the 1-hours glucose is ≥ 140 mg/dL , the patient undergoes a fasting 3-hours glucose tolerance test and GDM is diagnosed if two or more hourly glucose measurements are above specific value e.g.

- Fasting > [illegible] mg/dL
- 1 hr > 190 mg/dL
- 2 hr >165 mg/dL
- 3 hr> 145 mg/dL
- ≥2(ACOG ≥1)

Management of GDM

Tight glycaemic control is of utmost importance in pregnancy as poor controlled DM may cause serious problems for foetal and mother wellbeing .During early pregnancy due to poor control diabetes may ↑ the risk of abortion and congenial anomaly while later in pregnancy this may prone to polyhydramnios, preterm labour and patient may undergo C-section due to macrosomic baby . Additionally diabetic pregnant mother may develop or worsen the following complications like

- Diabetic retinopathy
- Worsening albuminuria
- Worsening renal failure that may not reverse after pregnancy
- Eclampsia (to ↓ its risk it is recommended to start her on low dose aspirin (75 mg) after 12 weeks
- Therefore it is recommended to carry out a panel of investigations in diabetic mother (fundaoscopy , ECG , 24 hours urine collection for total protein & creatinine clearance and HbA1c before conception)

ADA recommends against the use of metformin & glibenclamide in pregnancy and therefore insulin (regular & NPH) is the first line therapy while insulin lispro, aspart and detemir are also safe in pregnancy (category B).The mother should undergo OGTT 4-12 weeks after delivery and if

Scanned with CamScanner

OGTT is abnormal than it is should be repeated every 3 years in case of pre-diabetes while for established diabetic patients should have HbA1c 4-12 after pregnancy .BP target is <135/85. **Serum frutosamine should be done instead of HbA1c in pregnancy but unlikely** HbA1c it reflect glycaemic control for only preceding 1-2 weeks and its value is depended on serum albumin value . When normal serum albumin is 5g/dL than normal value of serum frutosamine is 200-285umol/L .Glycemic target in GDM (ADA)

- Pre-meal glucose ≤95 mg/dL (5.3mmol/L)
- 1 hour post-prandial ≤140 mg/dL(7.8mmo/L
- 2 hour post-prandial ≤120mg/dL(6.7mmol/L)

- **Diabetes in Cystic fibrosis patients**

Diabetes in cystic fibrosis patients is due to exocrine deficiency and it is recommended to carry out OGTT at the age of 10-year in these patient. If it is abnormal, the patient should be started on insulin, as a sole therapy .they should be monitored for detection of diabetes complication after 5 years of diagnosis of diabetes (instead of 10-15 years as recommended for general population) .

➢ **What are the measures that can prevent or delay the risk of type 2 diabetes? (How to↓↓ the risk of progression of pre-diabetes to overt diabetes)**

- Weight loss (by diet , walk and life style modification) 71%
- Metformin(in obese patient only) 31%

➢ **Vaccination Mandatory for Diabetic Patients (ADA)**

- Influenza , pneumococcal, HAV&HBV , COVID-19
- HPV (< 26 years , 3 doses over 6 months
- HZV (shingles) after 50-year 2 doses
- DPT
- Rubella vaccination before pregnancy

➢ **Glycemic Target in Diabetic Patients**

It depend on age, comorbids and previous episode of hypoglycaemia .the following targets are recommended for majority of the diabetic patients

- HbA1c <7 while in old age having CVS disease < 7.5
- Fasting 90-126 mg/dL
- Pre-prandial ≤ 80-130 mg/dL
- Post-prandial ≤180-200 mg/dL
- while 2 hours post -prandial (72-144 mg/dL)

In old and hypoglycaemic patients, it is recommended to have a less-strict target and vice versa.

➢ **Secondary Diabetes**

Endocrinopathies

- Cushing syndrome

Muscular Disorder

Myotonic dystrophy

Scanned with CamScanner

- Acromegaly
- PCOS
- Glucagonoma
- Thyroid disorder(spectrum of disorder)

Liopodystrophy
Tuncal obesity

Pancreatic disorders

Chronic Pancreatitis

- Cystic Fibrosis
- Haemochromatosis

Drugs

- Steroids
- Thiazide diuretics
- Beta Blocker
- Statin
- Tacrolimus (Calcineurin inhibitors)
- Anti –psychotic like olanzapine

Infection

CMV
Congenital Rubella

➢ **Hypoglycaemia**

It is defined as signs & symptoms and blood glucose level less than 70 mg/dL.
Signs & symptoms are due to autonomic system activation and deprivation of brain of glucose called neurolycopenia (like drowsiness, delirium and inability to concentrate).

Classification of hypoglycaemia

- Level 1 <70 mg/dL
- Level 2 < 54 mg/dL
- Level 3 Signs & symptoms and altered sensorium

Major causes and risk factors for hypoglycaemia in Diabetes

1. Medical causes

1. Rapid improvement in /or strict glycaemic control
2. Previous severe hypoglycaemia
3. Impaired awareness of hypoglycaemia
4. Long-duration type 1 diabetes
5. Duration of insulin therapy in type 2 diabetes
6. Lipohypertrophy at injection sites causing variable insulin absorption
7. Severe hepatic dysfunction
8. Impaired renal function
9. Inadequate treatment of previous hypoglycaemia
10. Terminal illness
11. Unrecognised other endocrine disorder, e.g. Addison's disease

2. Reduced intake of carbs

1. Gastroparesis due to autonomic neuropathy causing variable carbohydrate absorption

Scanned with CamScanner

2. Malabsorption, e.g. coeliac disease
3. Eating disorder (Bulimia nervosa and anorexia nervosa etc)

3. Lifestyle

- Exercise
- Irregular lifestyle
- Increasing age
- Alcohol and factitious
- Early pregnancy & breast-feeding

Management of hypoglycaemia

1) Self-treatment

People with diabetes who recognise developing hypoglycaemia is encouraged to treat immediately.

- Oral fast-acting carbohydrate (10-15 g) is taken as glucose drink, tablets, or confectionery, Repeat capillary glucose measurement 1-15 mins later. If still <4.0 mmol/L, repeat above treatment
- If blood glucose remains <70 mg/dL after three cycles (30-45 mins), consult with a doctor. Consider glucagon 1 mg IM or 150-200 ml 10% glucose over 15 mins IV
- once blood glucose is > 70 mg/dL, take additional long-acting carbohydrate
- modify and adjust the insulin dose

2) Someone help required

The means individuals are either unconscious or unable to treat hypoglycaemia themselves. Treatment is usually by a relative or by health care personnel

➢ **If patient is semiconscious / unconscious, parenteral treatment is required**

- IV 75-100 ml 20% dextrose over 15 mins (= 15 g; give 0.2 g/kg in children) or
- IV 150-200 ml 10% dextrose over 15 mins or
- IM glucagon (1 mg: 0.5 mg in children) - may be less effective in patients on sulphonylurea/under the influence of alcohol

➢ **if patient is conscious and able to swallow:**

- Give oral refined glucose as drink or sweets (= 25 g) or 1.5-2 tubes of Glucogel/Dextrogel or
- Apply glucose gel, /am, or honey to buccal mucosa
- Repeat blood glucose measurement after 10-15 mins and manage

➢ **Hyperglycaemia**

- Level 1 →200-250mg/Dl
- Level 2 →> 250

Different ways of glucose monitoring

- Intermittent blood sugar monitoring by glucometer
- **Continuous glucose monitoring systems are the Recent Advances that include**
- DexCom
- MiniMED

Scanned with CamScanner

- FreeStyle Libre (Abbott Diagnostic, collect 10-14 days data of RBS)

➢ **Management of Diabetes**

I. Weight loss

II. Exercise

II. Judicious use of Alcohol (have beneficial & harmful effects like ↓ the hypoglycaemic awareness &gluconeogenesis and therefore ↑ the risk of hypoglycaemia

I. Stop smoking

II. ↑ intake of nuts , water fruits and rotti ,↓rice

III. Avoid bakery items ,most of the underground vegetable .Avoid 'atherogenic diets or those that aggravate complications, e.g.high protein intake in nephropathy

IV. Anti-diabetes drugs & insulin

V. **Recommended % of energy intake in diabetic patients**

- Carbohydrate →50%:
  - Sucrose →up to 10%
- Fat (total)→ <35%:
  - n-6 Polyunsaturated<10%
  - n-3 Polyunsaturated :eat 1 portion (140 g) oily fish once or twice weekly
  - Monounsaturated: 10-20%
  - Saturated: <10%
- Protein→ 10-15% (do not exceed 1 g/kg body weight/day)
- Fruit/vegetable → 5 portions daily

➢ **Management of diabetes in special population**

A) Diabetes and Obesity

- 500-1000 calories deficit/day is recommended
- Weight reduction via life style modification (diet& exercise) followed by drug as an adjunct to life style changes
- Drugs available are orlistat(120mg TDS) , combination of low dose phentermine & topiramate, 5-HT_{2c} inhibitor Lorcaserin, combination of opioid antagonist naltrexone and adrenaline while more recently GLP-1 analogue that is gradually increased over period of time like Liraglutide(3mg/week **Saxenda®** only) and oral semaglutide(2.4mg/week **Ozempic ®**) are approved for weight loss .5% weight loss after 12 weeks is satisfactory and may indicate long-term weight loss with the drugs
- Bariatric surgery is by far the most effective long-term treatment for obesity and indicated for those with severe BMI > 40kg/m^2 or those with BMI > 35kg/m^2 and comorbids like Diabetes ,obstructive sleep apnoea and new guideline also recommend surgery at a lower weight in people with new-onset diabetes and BMI >30kg/m^2 .

B) DM and IHD

- BP target in Diabetes according to ADA is <130/80 while JNC-8 recommends BP target of < 140/90 .In case of proteinuria in hypertensive diabetic patients , the ACEs/ARBs are the first line irrespective of the age of patients

Scanned with CamScanner

- **Primary prevention of IHD in Diabetic patients**
  - No risk factors and age < 40-year statin is not indicated
  - Age< 40 years and there are risk factors (HTN , obesity ,& sedentary life style , smoking , family HX of IHD) moderate intensity(rosuvastatin20mg/atorvastatin 40mg) statin is indicated
  - Age>40 year and positive risk factors, high intensity statin ((rosuvastatin 40mg/atorvastatin 80 mg) is indicated and target is ≤70mg/dL.
- **Secondary prevention (established IHD, stroke and PDA)**
  - High intensity statin is indicated irrespective of Diabetes and age. If LDL is ↑↑ despite statin therapy then add Ezetimibe.
  - Statin is absolutely contraindicated in pregnancy
- **DM and antiplatelet agents**
  - It has no beneficial role in diabetic patients for primary prevention (primary prevention is only indicated for diabetic patients with high cardiovascular risk)
  - Aspirin(low –dose) is effective in ↓ cardiovascular morbidity and mortality in patients who have positive history of MI and stroke (as secondary prevention)
- **GLP-1 &SGLT-2 and CVS (IHD, HF and stroke)**
  - This agents ↓ cardiovascular morbidity and mortality in diabetic patients (while SGLT-2 has similar positive impact on cardiovascular morbidity and mortality in non-diabetic population as well)

(C) Diabetic Nephropathy

Screening for Microalbuminuria in Diabetic Patients

- Screening identifies incipient nephropathy in type 1 and type 2 diabetes; is an independent predictor of macrovascular disease in type 2 diabetes
- Risk factors include high blood pressure, poor glycaemic control and smoking
- Early morning urine is measured for the albumin: creatinine ratio (ACR), Micro albuminuria is present if
  Male ACR 2.5-30 mg/mmol creatinine
  Female ACR 3.5-30 mg/mmol creatinine
- An elevated ACR should be followed by a repeat test:
  There is established microalbuminuria if 2 out of 3 tests are positive
  An ACR >30 mg/mmol creatinine is consistent with overt nephropathy

Stages

- **Stage 1 Hyperfiltration**

Characterized by ↑ GFR and may be reversible

- **Stage 2(Silent or latent Phase)**

GFR remains elevated and most patients does not developed micro albuminuria for 10 years

Scanned with CamScanner

- **Stage 3(incipient nephropathy)**

Characterized by micro albuminuria (30-300mg/day) but dipstick negative

- **Stage 4(overt nephropathy)**

Persistent proteinuria >300mg/day and dipstick positive and hypertension is present in majority of cases and histology is positive for **Kimmelstiel-Wilson Nodules**

- **Stage 5(ESRD)**

GFR < 15 ml/min

Renal replacement therapy is indicated

Management

- The presence of established micro albuminuria or over nephropathy should alert the physician to take vigorous steps to ↓ risk of progression of nephropathy and cardiovascular disease .Following measure are recommended
  - Optimization of Glycemic control and blood pressure (ACEs/ARBs are the first line therapy as halving the amount of proteinuria with an ACEs-inhibitors or ARB result in a nearly 50% reduction in long-term risk of progression to end-stage renal disease)
  - Treat cardiovascular risk factors if any (as it is an independent predictors of macrovascular disease in type 2 diabetes)
  - GLT-1 analogue and SGLT-2 (can be used upto stage III CKD only and it also ↓the progression) can be use and if GFR is >30ml/min ,(GLT-1 analogue can be used upto CKD stage 4)while insulin should be initiated if GFR less than 15ml/min and is an indication for dialysis
  - Screening for diabetic nephropathy is warranted after 5-year of diagnosis of type 1 diabetes while all type 2 patients should be screen at the diagnosis and then at regular interval

D) What are the different types of insulin and their duration of action?

Duration of action (in hours) of various insulin preparations			
Insulin	**Onset**	**Peak**	**Duration**
Rapid-acting insulin analogues like → lispro, aspart, glulisine)	<0.5	0.5-2.5	3-4.5
Short-acting →Regular insulin	0.5-1	1-4	4-8
Intermediate-acting (Isophane (NPH), lente)	1-3	3-8	7-14
Long-acting bovine ultralente	2-4	6-12	12-30
Long-acting insulin analogues→ glargine, detemir, degludec	1-2	None	18-26

Scanned with CamScanner

E) Diabetic Retinopathy (DR)

- In type 1 diabetes , retinopathy is not detectable for the first 5-year after diagnosis while in type 2 diabetes , about 20% of patients have retinopathy at diagnosis and that is why type diabetic should be screened 5 year after the diagnosis while type 2 diabetic be screened at or shortly after diagnosis. However, close monitoring of women (regardless of the types of DM) is recommended during pregnancy (as it exacerbate during pregnancy).

Micro aneurysms on fluorescein angiography is the earliest sign of diabetic retinopathy

T1 DM

- Newly diagnosed DM →after 5 years
- From 5-10 years →annual
- More than 10 year →6 monthly

T2 DM

- Annual

Classification of Diabetic Retinopathy

Stage	Dilated Ophthalmoscopy Observable Findings	Severity
1	No abnormalities	No DR
2	Micro-aneurysms only	Mild non- proliferative DR
3	• Any of the following: • micro-aneurysms • retinal dot and blot haemorrhages • hard exudates or cotton wool spots • No signs of severe non-proliferative diabetic retinopathy	Moderate non-proliferative DR
4	• Any of the following: • more than 20 intra-retinal haemorrhages in each of 4 quadrants ○ definite venous beading in 2 or more quadrants ○ prominent intra-retinal microvascuar • abnormality (IRMA) in 1 or more quadrants No signs of proliferative retinopathy	Severe non- proliferative DR
5	One or both of the following: - Neovascularization - Vitreous/pre-retinal haemorrhage	Proliferative D

Except maculopathy all stages of retinopathy is more common in T1 DM than T2 DM

Management of Diabetic Retinopathy

- Glycemic control is the most important modifiable risk factor of diabetic retinopathy .Additionally , optimization of BP control , lipid disorder, renal function and quitting smoking also slow retinopathy progression
- Refer the patient to ophthalmologist for proper treatment

Scanned with CamScanner

- Macular oedema(but not ischemia) and exudate may respond to laser photocoagulation and intravitreal administration of VEGF inhibitors(like ranibizumab , bevacizumab etc it improve diabetic retinopathy at all levels of non-proliferative DR) or corticosteroid (triamcinolone ,dexamethasone implant) or vitrectomy
- Proliferative retinopathy is best treated with intravitreal injection of a VEGF or pan retinal photocoagulation. Proliferative retinopathy is not a contraindication (esp. after laser treatment) to treatment with thrombolytic agents like aspirin or warfarin unless there has been recent intraocular haemorrhage.

F) Diabetic Neuropathy

May be sensory(↓ perception of vibration sensation in gloves &stocking, loss of tendon reflexes in the lower limbs , paresthesia , pain & burning sensation) motor and autonomic neuropathy but all may be involved in various combinations so that clinically mixed syndromes usually occours.

Diabetic neuropathic cachexia is a condition characterized by a symmetric peripheral neuropathy associated with profound weight loss and painful dysesthesias affecting proximal part of lower limbs, hands, lower trunk .It is treated with insulin, and analgesic .This may be a manifestation of **diabetic amyotrophy**

Classification of diabetic neuropathy	
Somatic	Visceral (autonomic)
• Polyneuropathy: Symmetrical, mainly sensory and distal Asymmetrical, mainly motor and proximal (including amyotrophy) • Mononeuropathy (including mononeuritis multiplex)	• Cardiovascular • Gastrointestinal • Genitourinary • Sudomotor • Vasomotor • Pupillary

➢ **Management**

Sensory Neuropathy

Approved treatment options of sensory neuropathy include

- Duloxetine (tab Lyta) 60-120mg/day
- Nortriptyline (tab Sensival)25-150 mg/day
- Amitriptyline (Tab Amyline) 25-75mg/day
- Gabapentin(Tab Neogab)900-1800 mg/day
- Pregabalen is a less preferred drug (100-300mg/day)
- Capsaicin & 5% lidocaine patch

Motor Neuropathy

Glycemic control and supportive care

Scanned with CamScanner

Autonomic Neuropathy management

Cardiovascular	Sudomotor	Pupillary
○ Postural hypotension ○ Fixed heart rate ○ Resting tachycardia	○ Nocturnal sweats without hypoglycaemia ○ Gustatory sweating ○ Anhidrosis; fissures in the feet	○ Decreased pupil size ○ Resistance to mydriatics ○ Delayed or absent reflexes to light
Gastrointestinal	**Genitourinary**	**Vasomotor**
○ Dysphagia, due to oesophageal atony ○ Abdominal fullness, nausea and vomiting, unstable glycaemia due to gastroparesis') ○ Nocturnal diarrhoea ,faecal incontinence ○ Constipation, due to colonic atony	○ Difficulty in micturition, urinary incontinence. Recurrent infection due to atonic bladder ○ Erectile dysfunction and retrograde ejaculation	○ Feet feel cold, due to loss of skin vasomotor responses ○ Dependent oedema, due to loss of vasomotor tone and increased vascular permeability ○ Bulla formation

➢ **Gastroparesis**

- Metoclopramide(10mg TDS) before meals
- Erythromycin (250mg TDS)
- Botulinum Toxin into pylorus (↓pylorus sphincter resistance and ↑ gastric emptying)
- Gastric electrical stimulation (when resistant to pharmacological therapy)
- Diarrhoea associated with autonomic neuropathy may undergo spontaneous remission and if refractory you can advise loperamide(4-8mg/day) and or diphenoxylate with atropine
- Constipation may respond to stimulant laxative

➢ **Erectile Dysfunction**

It may result from neurological, vascular and or psychological or combination of all in diabetic patient

- Phosphodiesterase 5 inhibitors like sildenafil and vardenafil (may cause priapism). it is contraindicated in patients taking organic nitrates in any form
- External Vacuum therapy (Erec-Aid System)
- Intracorporeal injection into corpus cavernosum (like papverine with or without phentolamine and alprostadil)
- Psychological counselling and psychosexual therapy

➢ **Postural Hypotension**

- Avoid drugs like diuretics
- Compressive stockings
- Stand slowly from sitting position and change posture slowly
- Fludrocortisone and alpha- adrenergic agonist like midodrine

Scanned with CamScanner

- NSAIDs may have a role

➢ **Excessive sweating**

- Clonidine
- Topical antimusarinic agents like glycopyrrolate cream
- Antimusarinic drugs like propantheline, poldine and oxybutynin

➢ **Atonic bladder**

- Intermittent self-catheterization

G) Diabetic Foot

Care of the feet in diabetic patients	
Preventive Advice	
A) All Diabetic Patients	B) Moderate- and High-Risk Patients
o Inspect feet every day o Wash feet every day o Moisturise skin if dry o Cut or file toenails regularly o Change socks or stockings every day o Avoid walking barefoot	o Do not attempt corn removal o Check footwear for foreign bodies o Wear suitable, well-fitting shoes o Cover minor cuts with sterile dressings o Avoid high and low temperatures o Do not burst blisters o Avoid over-the-counter corn/ callus remedies
Podiatric Care	
• A podiatrist is an integral part of the diabetes team to ensure regular and effective podiatry and to educate patients in care of the feet	
Orthotic Footwear	
• Specially manufactured and fitted orthotic footwear is required to prevent recurrence of ulceration and to protect the feet of patients with Charcot neuro arthropathy	

- Foot is a common site of complications in diabetic patients and ulceration may occurs as result of trauma that may be trivial in the presence of neuropathy and or peripheral vascular disease with infection as secondary phenomenon following loss of protective epidermis (for pathophysiology see a reference book)
- Charcot neuro arthropathy is a progressive condition, with poor understood pathophysiology, affecting the bones & joints of the foot .Initially, there is inflammation followed by joint dislocation, subluxation and pathological fracture of the foot.

Management

It is divided into primary prevention and treatment of an active pathology.

The feet of people with diabetes should be screened annually. Two simple tests are required to grade risk, a 10 g monofilament (**for sensory function**) should be used to assess sensation at five point on each foot and foot pulses and if weak (go for →**ABP-index**)should be palpated

Scanned with CamScanner

(dorsalis pedis / posterior tibial) along with clinical scenario .While for ulcer/ wound broad spectrum antibiotics against gram positive organism and hyperbaric oxygen is recommended . Diabetic foot should be referred to a multidisciplinary foot team for proper management.

H) Formulation of insulin regimen

It is basically a weight-based regimen, most commonly, the insulin concentration in available formulation has been standardised at 100 U/mL. However due to certain condition like obesity etc there is increased daily insulin requirement ,Therefore, U200, U 300, U500 formulation of insulin is also available. Pre-mixed formulation are available that contain different proportions of regular and Isophane insulin like 70/30 (70% basal and 30% bolus), 60/40, 50/50. Insulin is started in the dose of **0.1 -0.5 units/kg** depending on the age and premorbid (80 kg patient will needs **40 units daily** e.g. 20 units basal and 20 bolus, 10 units of basal insulin is administered in morning and 10 units in evening (can be administered **as once daily**) while the 20 units of bolus insulin is administered 6 units TDS before meal and this is called **basal bolus regimen** and it is preferred regimen as it is **more physiological** .While another simple regimen is twice administration of short and intermediate –acting insulin in combination before breakfast (2/3rd) and pre evening meal (1/3rd) . ↑ the units of insulin gradually until the desired targets is achieved

Insulin-To-Carb Ratio (ICR)500/TDD =	#g of carbs covered by 1 unit of rapid-acting insulin
Insulin Sensitivity Factor (ISF)1800/TDD=	#mg/dL of glucose lowered by 1 unit of rapid-acting insulin
Example:	Insulin degludec 20 units daily & Novolog 10 units TID Total Daily Dose of Insulin (TDD) = 50 units ICR = 500/50 = 10 g carbs per 1 unit Novolog ISF = 1800/50 = 36 mg/dL BG lowered by 1 unit Novolog
If using regular insulin instead of rapid-acting: ICR = 450/TDD, ISF = 1500/TDD	

I) Hospitalized Diabetic Patient management.

- Blood glucose target is 140-180 mg/dL .Stop SGLT-2 3 days before surgery while metformin and other drugs at the day (morning) of surgery .Stop the bolus dose of morning, however, basal dose may be given with 2 hours blood glucose monitoring during surgery
- Post –op I/V infusion for neutralization of insulin
  - I. 1L 5% Dextrose with 16 units of insulin
  - II. 1L 10% Dextrose with 32 units of insulin
  - III. 1L 5% Dextrose with 16 units of insulin and 1 ampoule of KCL(GIK regimen post-op till NPO break

J) Surgical Procedure for Diabetic Patients

I. Bariatric surgery when indicated

II. Pancreatic cell transplantation

Scanned with CamScanner

III. Islet cell transplantation

K) HbA1c level Variation

➢ **Lower – than – expected levels of HbA1c**

(due to reduced RBCs lifespan)

- Sickle – cell anaemia
- GP6D deficiency
- Hereditary spherocytosis
- Chronic liver disease
- Splenomegaly
- Hypertriglyceridemia

➢ **Higher – than – expected levels of HbA1c**

(due to increased RBCs lifespan)

- Iron – deficiency anaemia
- Vitamin B 12\folic acid deficiency
- Alcohol dependence
- CRF
- Hyperbilirubenemia
- Splenectomy

L) Trials in Diabetes

I. The Diabetes Control and Complications trial (DCCT)

It was carried out in type 1 diabetic patients who were split into two groups, one with tight Glycemic control while another group have lenient or loose Glycemic control. After 7 years, the tight Glycemic group have 60% reduction in micro vascular and 40% macro vascular complication .However there was also weight gain and serious episodes of hypoglycaemia

II. The United Kingdom Prospective Diabetes Study (UKPDS)

In this trial type 2 DM patients were divided in two groups, one was on oral antidiabteic drugs or insulin while the other (controlled) group was advised dietary restriction only. The first group have ↓ microvascuar complications compare to the control group; however, there were more hypoglycaemic episodes and weight gain (in the first group).

M) Diabetic emergencies

➢ **DKA**

- **Steps of Management of DKA**

a) Fluid therapy (6 L N/S)
b) Insulin (0.1 unit/kg)
c) K replacement (1-2 ampoule in the 2nd liter of fluid)
d) Treat the underlying cause
e) DVT prophylaxis & Monitor for complications

Scanned with CamScanner

➢ **HONK**

a. Fluid (10-12 L deficit in 100kg patient)
b. Insulin (0.05units/kg / hr)
c. Treat the underlying cause (exclude MI, as it may be cause or consequence of HONK)
d. DVT prophylaxes & Monitor for complications
e. Poor prognostic factors are hypotension (<90mmHg) , hypothermia , severe hypernatremia (> 160mmol/L) , serum osmolality > 360mOsmol/kg , tacy or bradycardia and presence of other comorbids.

N) What is Dawn phenomenon & Somogyi Effect?

Dawn Phenomenon	Somogyi Effect(due to so much insulin)
Normal morning effect ↑ growth hormones & insulin levels	Rebound hyperglycaemia due to hypoglycaemia throughout the night
Treatment Increasing medication (i.e. increase basal insulin) or adjust timing to improve control	Treatment Decreasing medication (i.e. decrease evening insulin) or adjust timing to prevent hypoglycaemia
How to differentiate: check blood sugar in middle of night (i.e. 0300). High/normal indicates Dawn Phenomenon, low indicates Somogyi effect	

O) Oral anti-diabetic drugs and insulin

- Learn by heart all available oral anti-diabetic drugs and their MOA and major adverse effects

P) What are the Recent Advances in diabetes?

a. Continuous glucose monitors
b. Close loop system /artificial pancreas
c. **T1 DM→** Teplizumab (anti CD3 and it delay the onset of stage 3 in T1 DM who currently have stage 2 T1 DM)
d. **T2 DM → Trulicity** (Dulaglutide) &**Mounjaro** (Tirzepatide) **and Bexagliflozin** (SGLT-2 inhibitor FDA approved in January 2023) **while the most Recent Advances is once-weekly basal insulin icodec is recommended for treatment of diabetes by European regulatory authorities (march -2024)**

Q) Miscellaneous points

- HbA1c is > 7.5 → one oral antidiabteic drug
- HbA1c is > 8.5→ two oral antidiabteic drug
- HbA1c is > 9.5 →three oral antidiabteic drug
- If HbA1c is > 10 start insulin
- Oral antidiabteic improve HbA1c 0.5-1 units while insulin improve more than 1 unit
- **Monofilaments** , Monofilaments is applied gently until slightly deformed at five points on each foot .If the patient feels fewer than 8 out of 10 touches , the risk of foot ulceration is increased 5-10 fold

➢ **Trade names of few formulations**

- **Ozempic (semaglutide) 0.25mg, O.5 mg and 1mg**

Scanned with CamScanner

- **NovoRapid FlexPen** (Insulin aspart , each ml contain 100 units of insulin aspart, one Pre-filled pen contain 3mL equivalent to 300 U)
- **Levemir FlexPen** (insulin detemir , 5× 3ml and 100U/mL)
- **Humalog 50% KwikPen**(50% insulin lispro and 50% insulin lispro protamine suspension) while Humalog 25% contain 25% insulin lispro and 75% insulin lispro and Humalog contain only lispro
- **ApidraSoloStar** (insulin glargine /insulin glulisine 100units/ml -100units/ml
- **Novomix 30 FlexPen** 100U/ml(Biphasic insulin aspart e.g. Mixture of insulin aspart and protamine crystallised insulin aspart)
- **Lantus SoloStar** (insulin glargine 100 units /ml)
- **Trulicity** (Dulaglutide) 1.5mg /0.5 ml
- **Xultophy**(Insulin degludec +Liraglutide 100 units +3.6mg /ml)
- **Rvzodeg FlexTouch 100units/ml**(70% insulin Degludec and 30% insulin aspart

Scanned with CamScanner

APPROACH TO PALPITATION (Due to Hyperthyroidism)

P/C

Palpitation ...2months

HOPI (ODPARAV)

My patient presented with palpitation that is sudden in onset, progressive in nature and 2 months in duration and progressively worsening in time .Patient described his symptoms as feeling of racing of his heart in a regular pattern .Initially patient experienced 6-8 episodes/24 hours during exertion that lasted few minutes and resolved on taking rest and now for the last 2 weeks it occours on exertion as well as on rest for 10-15 minutes, resolve spontaneously and reoccur after some time. It has no specific exacerbating& reliving factors like holding breath. It is associated with excessive sweating, heat intolerance unintentional weight loss of 4-5 kg despite ↑ appetite; however, there is no association with coffee, drugs, foods and stress. However there is no HX of .....

Now exclude DDs of palpitation

1) Heart

- **M.I**

There is no HX of left sided chest pain that is associated with sweating, apprehension on the background of DM, HTN and IHD

- **Heart failure**

There is no HX of engorged neck vein, pedal oedema and SOB on exertion

- **Valvular Heart Disease**

There is no HX of recurrent childhood throat infection, monthly use of intramuscular injection.

- **Infective Endocarditis**

There is no HX of IV drug abuse and recent cardiothoracic surgery

2) Chest

- **Pneumonia**

There is no HX of high-grade fever, cough with rusty colour sputum production and chest pain

- **Asthma/COPD/B-2 agonists**

There is no HX of whistling chest sound and use of inhaler

- **Pulmonary embolism**

There is no HX of unilateral lower limb swelling, recent immobilization and surgery

3) GIT

- **Diarrhoea**

There is no HX of loose stool and dizziness on standing from sitting position

4) Endocrinology

- **Hyperthyroidism(see care)**
- **Pheochromocytoma**

There is no HX of episodic headache associated with raised BP and sweating

- **Hypoglycaemia**

There is no HX of Diabetes and low blood sugar level associated with palpitation, tremors and altered sensorium

Scanned with CamScanner

- **Carcinoid**

There is no HX of wheezy chest, flushing of face and loose motion

- **Addison**

There is no HX of darkening of complexion, abdominal pain and dizziness on standing from sitting position

5) Haematology

- **Anemia**

There is no HX of pallor of complexion, and blood loss due to any cause

6) Psychiatric disorder like panic attack

There is no HX of mood disorder and swinging of mood

7) Drugs like thyroxin, cocaine amphetamine and diuretics

Scanned with CamScanner

APPROACH TO NECK SWELLING (Due to Hyperthyroidism)

P/C

Neck swelling ...4 months

My patient presented with neck swelling that is slow in onset, progressive in nature and 4 months in duration. According to the statement of patient, it is non-painful and increased in the size progressively over the period of 3-4 months .Its surface is smooth/irregular and moving with swallowing. It has no exacerbating and reliving factors .it is associated with heat intolerance, excessive sweating. however, it is not associated with difficulty in swallowing, change in quality of voice and shortness of breath .However there is no HX

Now exclude DDs of neck swelling

a. **Thyroglossal Cyst** →patient denied HX of prominence of swelling on tongue protrusion
b. **Cystic Hygroma**→ patient denied HX of persistence of this swelling since birth or childhood
c. **Lymphoma** →patient denied HX of lumps& bumps in the body, low grade fever and ↓ appetite
d. **TB**→ patient denied HX of low-grade fever, nights sweat and cough
e. **Cat-scratch Disease** → There is no Hx of cat scratch
f. **Ludwig Angina** →there is no Hx of periodontal disease, sore throat and dental pain or abscess
g. **Infectious mononucleosis** →there is no HX of sore throat, body aches and conjunctival redness
h. **HIV** → there is no HX of IV drug abuse, high-risk extramarital sexual behaviour
(Whenever you need to ask specific question from a female (related to intimacy) always ask permission from the examiners
i. **Trauma** →there is no HX of recent neck surgery and Cannulation
j. **Thyroid disorder** like hypothyroidism & hyperthyroidism

➢ **CARE /RECA of Hyperthyroidism**

Causes of hyperthyroidism

Graves 'disease (most common cause) →there is no family HX of such disorder
Multinodular goitre→ there is no HX of lumpiness or neck swelling
Thyroiditis (including Hashimotos) →there is no HX of fever & painful neck swelling and HX of recent childbirth (post-partum thyroiditis)
Autoimmune disorder →there is no HX of white patch on skin, paleness of complexion and family HX of diabetes
Drugs →there is no HX of recent uptake of drugs like iodine, lithium and amiodarone
TSH-secreting pituitary adenoma→ there is no HX of headache and decreased vision in both eyes

Scanned with CamScanner

Systemic review of hyperthyroidism

a. CNS → anxiety, seizure and lack of sleep
b. Eyes → eyes bulging and double vision
c. CVS→ palpitation , ↑BP , chest pain and arrhythmias
d. Resp→ shortness of breath
e. GIT → diarrhoea , weight loss and ↑ appetite
f. Obs&Gyane→ oligomenorrhoea and amenorrhoea
g. Others →HX of excessive sweating, tremors , proximal myopathy (difficulty standing from sitting position & rising hands above the head) skin and nail changes

Now ask complications of hyperthyroidism

a. **Thyroid storm** →there is no HX of emergency hospital visit due to high-grade fever, agitation and confusion
b. **Heart Failure** → there is no HX of pedal oedema, distension of neck veins and shortness of breath
c. **Atrial fibrillation** →there is no HX of palpitation, irregular heart-beats and stroke
d. **Hyperthyroid Periodic paralysis** →there is no HX of lower limb weakness that improved after KCL infusion
e. **Osteoporosis** →there is no HX of bones pain, difficulty in standing from sitting position and fracture of bones on trivial trauma
f. there is no HX ↓ **libido** and **impotence**
g. **Gynaecomostia**→ there is no HX of excessive breast tissue growth
h. **Onycholysis** →there is no HX of loss or deformity of nails
i. **Hypothyroidism**→ due to treatment

Now ask

- ITP (investigations, treatment and procedures)
- Relevant PAM-HUGS-FOSS-TV –F

Examination Scheme

Vitals

GPE →warm sweaty hands, tremors, thyroid acropachy, Onycholysis (Plummer's nail) vitiligo and palmar erythema, pulse (techy and irregular), JVP and tongue protrusion,

Eyes→ look for proptosis, lid lag, extra ocular movements and scar of tarsorraphy and fundascopy (optic nerve compression) RAPD and colour vision

Neck→ examine the thyroid (size, surface, consistency, nodularity, tenderness, movement with swallowing, percuss and check pemberton sign for retrosternal extension) and auscultate over the gland

Chest→ including CVS (tacy loud S1, S3 and systolic murmur) resp system and also look for Gynaecomostia

Lower limb→ for pretibial myxoedema, proximal myopathy (also of upper limb) and reflexes

Resp and abdomen → no significance

Scanned with CamScanner

VIVA OF HYPERTHYROIDISM

➢ **How will you investigate this patient?**

- Baseline investigation like **CBC** →Macrocytic Anemia
- **TFTs**→ TSH,FT3 and FT4
- **Technetium(Tc-99m) pertechnetate** (graves may have normal or ↑ uptake while thyrotoxicosis from thyroiditis have ↓ uptake)
- **Radioactive Iodine Scan** (↑inGraves disease and toxic nodular goitre ,↓ in thyroiditis) all radioisotope testing is contraindicated in pregnancy and breast feeding
- Thyroid ultrasound → for palpable thyroid nodules **while color flow Doppler sologrаphy** can differentiate between type 1 amiodarone induced thyrotoxicosis (enlarged gland with normal to increased blood flow velocity and vascularity) from type 2 amiodarone induced – thyrotoxicosis (normal gland without ↑ vascularity)
- **MRI &CT scan of the orbit** →Graves ophthalmopathy affecting the extra ocular muscles
- **Graves' antibodies** →TSH-receptor antibodies (80-95%), anti-TPO (50-80%) and anti-Thyroglobulin (50-70%)
- **Hertel optometry(** it measures distance between eye ball and eyelid)≥ 5mm is significant Grave's' ophthalmopathy
- **ECG→ atrial fibrillation**
- **Dexa-Scan** → Detection of osteoporosis

What are the causes of hyperthyroidism?

- Grave's Disease
- Multinodular Goitre(MNG)
- Toxic adenoma
- Marine –Lenhart syndromes (graves' disease with functional nodules → grave's+ MNG)
- Autoimmune
- Drug→ anti-cancer drugs like tyrosine kinase inhibitor

What are the specific features seen only in Graves' disease?

- Eye sign like exophthalmos and opthalmoplegia (only in 30% of patients)
- Pretibial myxoedema
- Thyroid bruit
- Thyroid acropachy

How will you treat this patient?

Treatment of Grave's disease

Three options are available depending on the underlying cause, antithyriod drugs, radioactive iodine and or surgery

1. Antithyriod drugs

If age is <40-years, good compliance and there is no thyromegaly

a) **Carbimazole** 30-60mg once or twice daily,(this result in subjective improvement within 10-14 days) and when patient become clinically and biochemically euthyroid (6-8 weeks) 5-20mg for

Scanned with CamScanner

18-24 months . However, 50-70% will* subsequently relapse within 2 years of stopping the treatment .Relapse is more common (risk factors) young age, male gender, presence of goitre and high anti-TSH antibodies level

b)Block and replace regimen →in this regimen we block thyroid hormone synthesis with carbimazole 30-40mg and once patient is euthyroid then we add levothyroxine 100-150 mcg daily as replacement therapy (it is primarily indicated in patients who fluctuate between hyper and hypothyroidism at successive review appointments)

c) Propylthiouracil 400-600mg followed by 100-200mg TDS in case carbimazole is not tolerated or indicated (pregnancy & breastfeeding)

d) B-blocker like propranolol (60-320mg) is indicated for tremors, excessive sweating, tachycardia, and it effectively treat thyrotoxic hypokalemic periodic paralysis .Target heart rate (pulse) is < 90 while in case of atrial fibrillation < 105/min

d) Adverse effects Carbimazole →rash (most common), Agranulocytosis (reversible) alopecia, cholestatic jaundice, hypoglycaemia and nephrotic syndrome. **Propylthiouracil**→ small but definite risk of hepatotoxicity, lupus, arthritis, aplastic Anemia, thrombocytopenia and hypoprothrombinemia

2) Radioactive Iodine I^{131} (RAI)

Iodine I^{131} is administered orally and it is trapped in thyroid where it emits beta and gamma radiation .it provide effective temporarily treatment for thyrotoxicosis of any cause and particularly in patients who are symptomatically very thyrotoxic. The variable radio-iodine uptake and radiosensitivity of the glands render the the choice of dose empirical, however, most commonly 400-600MBq (approx. 10-15MCi) is administered. This regimen is effective in 75% patients in 4-12 weeks .Carbimazole should be stopped 3 days before the therapy (it prevent organification of I^{131} in the gland) and should be avoided until 48-hours after administration of I^{131} If thyrotoxicosis persists after 6 months, a further dose of I^{131} is usually given.

Precautions

- the presence of Graves ophthalmopathy is a relative contraindication to I^{131} therapy while in case patients with Graves ophthalmopathy has to be treated with I^{131}, they should be considered for prophylactic prednisolone (20-40mg) for 2 months following I^{131} therapy.
- Active smokers should be advised to quit smoking before I^{131} therapy (as it may exacerbate ophthalmopathy and ↓ effectiveness of prednisolone treatment) while smokers should be prophylactically start on prednisolone
- In women of reproductive age , pregnancy must be excluded before I^{131} therapy and should be avoided for 6 months thereafter .men are also advised against fathering children (due to abnormal spermatozoa) for 6 months and use contraceptive method during that time .Additionally breastfeeding mother should also avoid this mode of treatment
- Majority of patient treated with I^{131} will develop hypothyroidism and therefore follow-up with measurement of TSH and FT4 is indicated

Scanned with CamScanner

3) Thyroid Surgery

It is indicated in large goitre, non-compliance, patient who refuses RAI & drugs and in graves ophthalmopathy. Before surgery patient should be render euthyroid by antithyriod drugs (& beta-blocker with HR <90/min) .Additionally, to ↓ vascularity, size and hormone synthesis of thyroid gland, K-iodide (60mg TDS or 2-3 drops 6 hourly) is use preoperatively for 10 days.

Name of surgery

- **Sub-total thyroidectomy** (total resection of one lobe and subtotal resection of other lobe leaving only 4g thyroid tissue) in this surgery 80% patients are become euthyroid , 15% hypothyroid and **5% still thyrotoxic and therefore**
- **Near-total thyroidectomy** (only a small –portion of thyroid adjacent to laryngeal nerve is left) is new approach by most surgeon due to maximises the cure of thyrotoxicosis but at the cost of permanent hypothyroidism

Complications of surgery

- Hypothyroidism
- Hypoparathyroidism
- Laryngeal nerve palsy resulting in vocal cord palsy .In case bilateral nerve damage airway obstruction may develop and may require intubation and tracheostomy

How will you manage Graves's ophthalmopathy?

It is immunologically mediated disorder, for pathophysiology see a reference book. Eye disease is detectable in upto 50% of thyrotoxic patients at presentation, but active eye inflammation may occours before or after thyrotoxic episodes .So it may occours during any phase of Graves' disease (hyper, euthyroid and hypo) .it is more common in smoker and exacerbate with poor control of thyroid function (esp. hypothyroidism) ,ethanol injection into thyroid nodules . It worsen following I^{131} therapy (and therefor it is relative contraindication for I^{131} therapy) and with thiazolidinedione e.g. pioglitazone

Stages

- **Inflammatory stage**
  This is characterized by active lymphocytic infiltration into retro bulbar tissues .this stage may last for 18-36 months
- **Chronic fibrotic stage**
  It is also called burned out phase .In this stage exophthalmos is medically resistant to glucocorticoid treatment.

DDs

- Congenital proptosis
- Asymmetrical orbital protrusion
- Dural carotid-cavernous sinus
- Ocular myasthenia (ptosis rather than lid retraction)

Scanned with CamScanner

Treatment

- Supportive care to protect the eye like wearing the glasses, artificial tear covering the eyes during sleep and advise to stop smoking
- Specific therapy include , selenium (100mcg BD 6months) for mild thyroid eye disease and it may slow down the progression
- Intravenous pulse methylprednisolone 500mg weekly for 6 weeks followed by 250mg weekly for 6 weeks ,while oral dose of prednisolone is 40-60 mg daily tapering over period of several weeks .Higher dose(80-120mg) is indicated in case of optic nerve compression ,However , prednisolone is less effective in smoker
- Steroid resistant acute thyroid disease may be treated with retro orbital injection of rituximab ,intravenous tocilizumab (interleukin6 -receptor antagonist) and teprotumumab (Monoclonal antibody that binds insulin –like growth factor-1 receptor)
- Retro bulbar radiation therapy for progressive active exophthalmos while it is less effective in patient with chronic proptosis & orbital muscles restriction .it may cause radiation induced retinopathy particularly diabetic
- Diplopia should be treated conservatively (with prism)in active stage and when proper surgery is done when disease is in remission for at least 6 month, however, acute decompressive surgery may be indicated for severe vision threatening disease

How will you treat thyrotoxic hypokalemic periodic paralysis?

It may last for 7-73 hours .start oral propranolol (3mg/kg in divided doses), antithyriod drugs and normalized the serum potassium and phosphate (not through IV route).avoid intravenous dextrose and oral carbohydrate rich diet as it may exacerbate the condition.

How will you treat hyperthyroidism in pregnancy?

- As there is risk of congenital anomaly (2%) with currently available antithyriod drugs, therefore, it is recommended for all women who are planning pregnancy, to opt for definitive therapy like surgery or RAI before conception. As anomalies risk is comparatively low with PTU than carbimazole, therefore, women should be treated with PTU (50-150mg/day) immediately pre-pregnancy and during first trimester and should be switched to methimazole (5-15mg/day) in the 2nd trimester. Low possible dose should be used to avoid hypothyroidism in the infant
- Fetal ultrasound should be done at 20-32 weeks of gestation to look for fetal goitre that may signify drug induced hypothyroidism and needs treatment
- FT4 target is 1.5 times of pre-pregnancy level
- Subtotal thyroidectomy in 2nd trimester is indicated when there is severe adverse effects of drugs , higher dose requirement to control the disease (methimazole ≥30mg/day, PTU ≥450mg/day) and uncontrolled disease due to non-compliance
- Breastfeeding is allowed and it is recommended to take medication just after breast feeding

Scanned with CamScanner

How will you treat atrial fibrillation due to hyperthyroidism?

- Atrial fibrillation may occours upto 10% cases of thyrotoxicosis and the incidence is more with advancing age. Ventricular rate in atrial fibrillation induced by thyrotoxicosis is less influenced by digoxin (↑ doses may be required), however, it respond well to beta-blocker .Effective treatment of thyrotoxicosis may spontaneously revert to sinus rhythm in 50-60% of cases, meanwhile, there is a 60% chance that atrial fibrillation will recur, despite normal thyroid function. Electrical cardioversion is less effective while patient is thyrotoxic and those with persistent atrial fibrillation may have elective cardioversion following anticoagulation 4 months after resolution of hyperthyroidism(euthyroid state) and if still resistant than sub-total thyroidectomy is indicated
- Thromboembolic complication are common in thyrotoxic atrial fibrillation and therefore low dose (due to accelerated clearance of vitamin-k dependent clotting factors) anticoagulant like warfarin is required

Graves's dermopathy (Pretibial myxoedema) treatment

It is characterized by raised pink –coloured or purplish plaques on the anterior aspect of leg, extending on to the dorsum of the foot. The lesion may be itchy and skin may have a peau d orange appearance .treatment is application of topical steroid with night -time plastic occlusive dressing.

How will you manage thyrotoxic crisis (thyroid storm)

- It is rare but life-threatening complication of thyrotoxicosis and medical emergency having 10% mortality .Burch-Wartofsky may be used to help establish the diagnosis. Early recognition and treatment is of utmost importance .most common precipitating factor is infection in unrecognized or inadequately treated thyrotoxic patient's .it may also occours shortly after thyroidectomy in thyrotoxic patient or after I^{131} therapy.
- It is managed in ICU .patient should be rehydrated and oral carbimazole (15-25mg 6 hourly) or PTU (150-250mg hourly) followed by K-iodide (10 drops TDS/day) 1 hour later (↓ hormones synthesis and conversion of T4 to T3) .To control the heart rate, propranolol (20-120mg IV 6 hourly) is given. Hydrocortisone (50mg, 6 hourly it (↓ hormones synthesis and conversion of T4 to T3) should also be initiated
- To control ↑ temperature, cold sponging and intravenous paracetamol is recommended, however, aspirin should be avoided (as it displaces FT4 from thyroxin binding globulin.
- If resistant to above measures , emergency surgical thyroidectomy is an option
- Cardiogenic shock may be managed with supportive care including vasopressors, mechanical ventilation, dialysis, and extracorporeal membrane oxygenation.

➢ *If the patient is unconscious or agitated, carbimazole may be given rectaly*

What is Pendrid Syndrome?

It is autosomal recessive disorder of defective iodine uptake characterized by sensor neural deafness and enlarged thyroid (Goitre).

Treatment of toxic solitary thyroid nodules

Scanned with CamScanner

Toxic solitary nodules are mostly benign but may be very rarely malignant and therefore, FNA biopsy is indicated. Medically therapy is same as described in Graves' disease; methimazole dose should be adjusted to keep the TSH slightly suppressed (to ↓ risk of TSH stimulated nodule growth). **Surgical treatment is** indicated for patient aged < 40, and nodules suspicious for malignancy. Patient should be made euthyroid before surgery. **RAI** is indicated when age is> 40 and unable to undergo surgery and is the **preferred therapy** .if the patient has been receiving methimazole long time before I^{132}, the TSH should be kept slightly suppressed in order to reduce the uptake of I^{132} by normal thyroid .

Treatment of Toxic Nodular Goiter

Medical therapy for patient with toxic nodular goiter is same as outlined for graves, it revers hyperthyroidism but do not shrink the goiter and if drug is stopped there is 95% recurrence of hyperthyroidism .**Surgical therapy is the definitive treatment** for large toxic goiter causing pressure symptoms or cosmetic reason, after making patient euthyroid (not with K-iodide) . **RAI** may be used to treat patients with toxic nodular goiter .patient follows a low-iodine diet in order to enhance the thyroid glands uptake of I^{132}. High doses of I^{132} are required. This therapy may cause hypothyroidism or recurrent thyrotoxicosis and need close monitoring .Rarely, Grave's ophthalmopathy may occur following I^{132} therapy for multinodular goiter.

Treatment of thyroiditis induced hyperthyroidism

- Patients with thyroiditis of any aetiology (subacute, postpartum or silent) are treated conservatively. To control the heart rate, propranolol is initiated with target HR <90/min , ipodate sodium or Iopanoic acid (500mg) daily for 15-60 days until the serum FT4 level get back to normal .However , antithyriod drugs are ineffective (due to ↓ thyroid hormone synthesis) .Pain can be managed with NSAIDS or corticosteroid .
- Women suffering from **post-partum thyroiditis** are likely to have anti-TPO antibodies in serum in early pregnancy. Women with symptomatic thyrotoxicosis presenting for the first time within 12 months of childbirth is likely to be due to post-partum thyroiditis and is confirmed by minimal radio-isotope uptake .Post-partum thyroiditis tends to recur after subsequent pregnancies and ultimately patient progress over a period of years to permanent hypothyroidism

Eponyms of Eye Signs In Thyroid Disease

- Lid lag of upper eyelid→ **von Graefe s sign.**
- Lid lag of lower eyelid→ **Griffth, s sign.**
- Lid retraction →**Dalrymple, s sign.**
- Absence of wrinkling of forehead on upward gaze → **Joffroy, s sign.**
- Impaired convergence of eye→ **Mobius, sign**
- Infrequent blinking→ **Tellwag, s signI.**
- Paralysis of extra ocular muscle→ **Jendrassik, s sign:**
- Weakness of at least one extra ocular muscle→ **Ballet sign.**
- Tremor of closed eyelid→ **Rosenbach, s sign.**

Scanned with CamScanner

Interpretation of TFTs

Primary hyperthyroidism →↓TSH, T3+T4↑

Secondary hyperthyroidism →↑TSH, ↑T3+T4

Subclinical hyperthyroidism →↓TSH, normal T3 and T4

(Do not treat subclinical hyperthyroidism until complications develops)

Scanned with CamScanner

HYPOTHYROIDISM

P/C

1. Neck swelling or
2. Fatigability or
3. Lower limb swelling

HOPI and (ODPARA-V) of each presenting complaint

Systemic review

1. CNS → ask about depression, memory impairment and slowness of movement
2. Eyes → dryness and periorbital puffiness
3. CVS→ chest pain (MI due to↑ cholesterol) and SOB (Heart failure)
4. GIT→ ↓ appetite, ↑ weight and constipation
5. Others

a. Men → ↓libido
b. Women → excessive menstruation
c. Dry rough thick skin
d. Cold intolerance
e. Hair loss in scalp and eyebrow
f. Coarse facial feature
g. Excessive sleepiness (somnolence)
h. Extreme tiredness

Causes / risk factors of hypothyroidism?

See viva section

Complications of hypothyroidism

a. **Myxoedema Coma** →Hx of emergency admission with very low temperature,↓ GCS, generalized body swelling and low heart rate
b. **Hypothermia**
c. **Megaloblastic anaemia**→ paleness of complexion
d. **Obstructive sleep apnoea**→ Hx of snoring during sleep , daytime tiredness and sleepiness
e. **Heart failure**
f. **MI** → due to ↑ fasting lipid profile
g. **Hypokalemic periodic paralysis**
h. **↑ Susceptibility to pneumonia**
i. **Infertility**
j. **Megacolon**
k. **AKI** → due to rhabdomyolysis
l. **Carpale tunnel** syndrome

Examination

Vitals

GPE → coarse dry skin, pulse (Bradycardia), loss of outer third of eyebrows, puffy lower eyelids, Xanthelasma, JVP, anemia, hoarse voice, large tongue and non-pitting edema

Scanned with CamScanner

Thyroid →as discussed previously
CVS → heart failure and pericardial effusion
Abdomen → ascites
CNS → mental sluggishness, proximal weakness, delayed ankle reflex, cerebellar sign (at
and carpal tunnel syndrome and peripheral neuropathy

VIVA OF HYPOTHYROIDISM

Hypothyroidism may also present as neck swelling (thyromegaly) and you have to follov
scheme discussed earlier with hypothyroid features in the statement.

What are the causes of hypothyroidism?

a) Autoimmune

- Hashimoto's thyroiditis →most common cause
- Primary atrophic hypothyroidism
- Grave's diseases with TSH receptor blocking antibodies

b) Iodine deficiency

c) Iatrogenic like

- Post thyroidectomy
- Post-radioactive iodine ablation
- Drugs like lithium , amiodarone ,carbimazole & PTU

d) **transient thyroiditis**

- Subacute thyroiditis
- Post -partum thyroiditis

e) **Secondary hypothyroidism**

- TSH deficiency
- Prolong infusion of dopamine can induced secondary hypothyroidism(↓↓TSH production) ar
  same is true for mitotane and Bexarotine

f) **Congenital**

- Thyroid aplasia
- Dyshormonogensis

g) **Infiltrative**

- Riedel's thyroiditis
- Amyloidosis & sarcoidosis

How will you investigate this patient?

a. **CBC**→(Anemia, all 3 types are possible)
b. **S.E**→ (↓ Na, dilutional) and to check associated hypoadrenalism (↑K)
c. **Fasting lipid profile** →(↑TG)
d. **RBS** →to screen for other autoimmune disorder)
e. **ECG**→ sinus bradycardia & low voltage complexes

Scanned with CamScanner

f. **Serum prolactin (↑**
g. **TFTs→** ↑TSH and low T4(T3 is not significant in hypothyroidism)
h. **Thyroid scan**
i. **Neck ultrasound** →(size , number & characteristic of nodules like solid and cystic and retrosternal goiter)
j. **Thyroid peroxidase antibodies(anti-TPO)→** (90-100%) but it make no difference on management therefore ,once hypothyroidism is confirmed ,there is no need to investigate certain antibodies

(Anti-TPO> anti-thyroglobulin >anti-TSH)

➢ **Treatment of primary hypothyroidism**

(Hashimoto's thyroiditis)

Treatment is with levothyroxine (1.6mcg/kg/day) replacement for lifelong in most of the cases .Initially low dose levothyroxine is initiated (50mcg for 3 weeks → then 100mcg for 3 weeks and followed by 150mcg), however, in young patient it is safe to start them on higher dose. The dose should be adjusted to maintain TSH within normal range and TSH should be repeated at least 6 weeks after dose adjustment. Symptomatic improvements occours in 2-3 weeks Reduction in weight loss & periorbital puffiness improve quickly; however, restoration of skin colour, hair texture and restoration of any effusion may takes 3-6 months. Some studies suggest levothyroxine should be taken before beds and with vitamin C supplements to maximise its absorption.

- **Hashimoto's thyroiditis is associated with thyroid lymphoma**
- Hashimoto's encephalopathy is extremely rare and present with altered mental status, myoclonus and ataxia. it is a steroid responsive encephalopathy

➢ **Treatment of hypothyroidism in pregnancy**

Pregnant women require ↑ dose of levothyroxine (35-50%) from early pregnancy .it is recommended to maintain TSH result within the trimester-specific reference range.
(Normally TSH falls in the first and second trimester and increases in 3rd trimester with subsequent fall in FT4 and FT3 in the 3rd trimester).

➢ **Treatment of Postpartum thyroiditis (PPT)**

It is a variant of chronic autoimmune thyroiditis (Hashimoto thyroiditis).Post –partum thyroid dysfunction is said to occur in up to 10% of women during the first year after delivery .It tends to occur within the 4 months of delivery by transient hyperthyroidism followed by a hypothyroid phase at 3 to 6 months followed by spontaneous recovery in one third of cases within 6-12 months of delivery, although upto 40% eventually go on to develop permanent hypothyroidism. .Management is based on symptomatic treatment using beta-blocker like propranolol for symptomatic relief of tremor & anxiety and observation for the development of persistent hypo or hyperthyroidism. In post-partum hypothyroidism, low dose thyroxine (50mcg) may be used to allow spontaneous recovery with testing after 6 months of therapy.

Scanned with CamScanner

PPT→ Hyperthyroidism→ Hypothyroidism →spontaneous recovery in 1/3rd or permanent hypothyroidism (40%).

➢ **Treatment of Hypothyroidism in IHD patients**

Higher dose of levothyroxine may prone these patients to exacerbation of cardiac ischemia, infarction and sudden cardiac death. Therefore, it is strongly recommended that IHD-patient should be started on very low dose (25ug/day) thyroxin and gradually increased (under strict supervision) until TSH value become within normal range .PCI may be indicated if angina is exacerbated by levothyroxine therapy.

➢ **Treatment of Myxoedema Crisis**

It is severe; life-threatening manifestation of hypothyroidism with high mortality rate, with treatment mortality is approx. 20-25% while without treatment it is 100%

- Intravenous T3 loading (liothyronine) 5-20mcg followed by 10mcg TDS for the first 48- hours while alternative approach is levothyroxine 500mcg loading dose followed by 50-100mcg intravenous daily .low dose is indicated in IHD patients
- Intravenous 5% dextrose saline for hypoglycaemia
- Hydrocortisone 100mg intravenously TDS (for suspected concomitant adrenal insufficiency)
- Broad-spectrum antibiotic in case of infection
- Active rewarming(blanket) for hypothermia
- Controlled rehydration and if BP still low, inotropes may be needed.
- ABGs for p_aO2 and patient with high PCO2 may need ventilation
- Symptomatic hyponatremia should be treated with boluses of 100ml of 3% NaCL with intravenous furosemide 20-40mg to promote water diuresis

➢ **Subclinical hypothyroidism**

Characterized by raised TSH and serum concentration of T3 and T4 are at the lower end of normal value. Treatment is indicated when there is positive antibodies and TSH > 10 mIU/L .the risk of progression to overt hypothyroidism is 20% per year.

➢ **What is sick euthyroid syndrome?**

In this syndrome, which is also known as non-thyroidal illness, it is said everything is low like TSH, T3 and T4 in sick euthyroid syndrome .Being a variable condition and many different results can be seen on thyroid testing and therefore, it is wise to avoid performing thyroid tests unless there is clinical evidence of concomitant thyroid disease.

Mention Thyroiditis names or types of thyroiditis

- Hashimotos thyroiditis also called chronic lymphocytic thyroiditis
- Postpartum thyroiditis. these two are part of auto immune thyroiditis
- De Quervains thyroiditis also called granulomatous thyroiditis or giant cell thyroiditis
- Infection(suppurative) thyroiditis
- Riedel thyroiditis also known as IgG_4-related thyroiditis
- Painless (silent) sporadic subacute thyroiditis (may be due to amiodarone and immunotherapy)

Scanned with CamScanner

How will you treat Riedel Thyroiditis?

- Short-term steroid for relieving pain and compression
- Tamoxifen 20mg BD for years and if not improving then
- Rituximab 375mg

What do you know about amiodarone and thyroid?

Amiodarone is anti-arrhythmic agent that has a structure that is similar to that of T4. 200mg of amiodarone 75mg of iodine and it also has a cytotoxic effect on thyroid follicular cells and inhibits conversion of T4 to T3. Upto 20% of patient's receiving amiodarone develop hypo or hyperthyroidism and therefore thyroid function should be monitored closely

Amiodarone –induced hypothyroidism (AIH)

The pathophysiological of amiodarone induced hypothyroidism (AIH) is thought to be due to the high iodine content of amiodarone causing a **Wolf –chaikoff effect** (it is an auto regulatory phenomenon where thyroxine formation is inhibition due to high levels of circulating iodide) .In other words iodine driven inhibition of thyroid hormone synthesis.

Amiodarone may be continued if this is desirable especially in causes of VT as it would be unwise to withdraw amiodarone suddenly, .therefore it is recommended to continued amiodarone and add thyroxine.

The typical results of amiodarone –induced hypothyroidism that inhibits the peripheral conversion of T4 to T3

↑TSH, low T3 and normal or elevated T4.

As T3 is the most active thyroid hormone, the low T3 feedbacks at the pituitary level results in increase TSH secretion.

Amiodarone-induced thyrotoxicosis (AIT)

Amiodarone-induced thyrotoxicosis (AIT) may be divided into two types:		
	AIT type 1	**AIT type 2**
Pathophysiology	Accelerated thyroid hormone synthesis secondary to iodide load. **(Jod Basedow effect).** Occurs in patients with underlying latent thyroid pathology.	Amiodarone-related destructive thyroiditis with effect directs of amiodarone on the follicular cells, with breakdown of cells and therefore release of preformed thyroid hormones T4 and T3. This is a direct toxic effect of amiodarone on the thyroid follicular cells, and occurs in patients without underlying thyroid disease
		Clinically tenderness

Scanned with CamScanner

Goitre	Present	Absent
Duplex US on thyroid for blood flow (is the most useful to differentiate between both types)	Increase	Decrease
iodine-131 uptake scan	Normal or high	Low or none
Thyroid Autoantibodies	Positive	
IL-6		High IL-6
99mTc-sestamibi scan	Normal or ↑ uptake	↓ uptake
Management	Carbimazole 40 mg OD or K perchlorate or lithium carbonate or or Surgery	Corticosteroids (prednisolone 40 mg/d)

Unlike in AIH, amiodarone should be stopped if possible in patients who develop AIT and if necessary other anti-arrhythmic could be used to maintain sinus rhythm such as sotalol or flecainide (if not contraindicated).
If amiodarone cannot be withdrawn then total thyroidectomy should be considered

What are the Recent Advances?

Desiccated natural porcine thyroid preparations containing both T3 &T4. About 65mg (1 grain) of desiccated thyroid is equivalent to 100mcg of levothyroxine

What are the types of thyroid cancer?

- Papillary (70%) →excellent prognosis
- Follicular (20%)→prognosis is good if resectable
- Medullary (5%) →part of MEN2 and secrete calcitonin
- Anaplastic (<5%)→ very poor prognosis
- Lymphoma (2%)→almost always non-Hodgkin lymphoma associated with hashimoto's

Scanned with CamScanner

APPROACH TO WEIGHT GAIN (Due to Cushing syndrome)

P/C

Weight Gain→ 5 months

ODPARAV (HOPI)

My patient who is a newly diagnosed diabetic & hypertensive presented with weight gain for the last 5 months, it is of gradual in onset and progressively worsening with time .According to the patient, he has gained 20-25kg weight despite normal diet and routine physical activities. Patient further stated that it is worsening with time and does not respond to any change in the physical activity or low calories diet .Additionally, beside weight gain, patient also complaining of excessive hair growth on body particularly on face, moon like face, easy brusibility and abdominal striae .However , there is no HX of .....

DDs

1. **6 Cs** as discussed in abdominal distension as part of generalized body swelling like
   CLD →CKD →CCF→ Cor Pulmonale →Cancer and chronic diarrhoea
2. **Endocrine causes**
   a. **Hypothyroidism**→ Patient denied HX of cold intolerance ,constipation and pale rough skin
   b. **PCOS** → patient denied irregular menses and past HX of cysts in ovary on ultrasonography (Cushing syndrome may also cause menstrual disturbance)
   c. **Insulinoma** →patient denied early morning sweating, blurring of vision and tremors (symptomatic hypoglycaemia)
   d. **Cushing syndrome →long case**
3. **Abdomino-Pelvic Mass**→ patient denied lumps & bumps in the body and heaviness in abdomen.
4. **Drugs** →patient denied prolong use of Insulin , Epival and Hakeemi medication(steroids)
5. **Metabolic syndrome** →patient denied family HX of obesity

CARE /RECA of Cushing syndrome

1. **Iatrogenic cushingiods** → patient denied prolong used of hakim medication and/or steroid for chronic lungs (like Asthma /COPD) or joints problems (RA& SLE).(Iatrogenic steroid is the most common cause of hypercortisolism)
2. **CA lung (SCLC) & bronchial carcinoid** → patient denied HX of blood in sputum, weight loss and hoarseness of voice
3. **Pituitary mass (Cushing disease) 70%**→ patient denied HX of headache that is worse in the morning and associated with ↓ visual acuity. (the most common cause of cushing syndrome)
4. **Pseudo Cushing**→ there is no HX of chronic alcohol intake and or HX of major depressive illness
5. **Adrenal Mass (adenoma 15% & carcinoma 5%)** →there is no HX of abdominal mass associated with muscle weakness and virilisation

Scanned with CamScanner

6. **Ectopic ACTH production due to CA lung, bronchial carcinoid and other neuroendrine tumour's→** no HX of darkening of skin associated with muscles weakness

Complications of Cushing syndrome

a. DM
b. HTN
c. Psychosis
d. Cataract
e. IHD like MI and dilated cardiomyopathy
f. Peptic ulcer
g. Compression fracture of vertebrae
h. Osteoporosis
i. Renal stones
j. Proximal myopathy
k. Recurrent infection & poor wound healing
l. Hirsutism
m. ↑ blood clotting
n. Centripetal obesity

Now ask relevant

ITP & PAM-HUGS-FOSS-TV-F

Examination scheme

Vitals

GPE → clubbing ,pink prick marks , numbness and tingling (carpal tunnel)skin atrophy, striae, fungal infection of skin folds and nails, telangiectasia, oral thrush, moon face, central obesity with relative thin limb

Eyes

- Cataract
- Filed defects
- check visual field (for pituitary tumor)
- fundascopy (to look for optic atrophy, papilledema, signs of hypertension and diabetic retinopathy)

Face, neck and back

- buffalo hump and supra-clavicular fat pads
- acne and hirsutism,
- plethora
- acanthosis nigricans,

Abdomen →thinning of skin, purple striae and epigastric mass due to CA-pancreas
Resp → look for evidence of asthma /COPD /ILD and CA lung
MSK→ bruising, wasting of the limbs and proximal myopathy
CNS →same as MSK, scar at the back (adrenalectomy), spinal tenderness and deformity (osteoporosis and vertebral collapse)

Scanned with CamScanner

CVS → no significance

Based on HX and examination, my clinical diagnosis is (or differential diagnoses are)

- Cushing syndrome due to …
- Hypothyroidism
- PCOS or pseudo Cushing

Scanned with CamScanner

VIVA OF CUSHING SYNDROME

How will you investigate this patient?

CBC →leukocytosis and↑ MCV may point to pseudo Cushing due to alcoholism
Serum electrolyte →
Blood glucose level → may be raised
Lipid profile → dyslipedemia
Oestradiol→ low Oestradiol exclude PCOS
TSH → normal value excludes hypothyroidism
Dexa scan → osteoporosis
Specific tests → see below

How will you establish the diagnosis of Cushing Syndrome?

The diagnosis of Cushing is a two -step process

a. To establish whether the patient has Cushing syndrome
b. To define its aetiology

A. Establishing the presence of Cushing syndrome

In-patient where there is appropriate clinical suspicion Cushing syndrome is confirmed by using two of three main tests

1. Failure to suppress serum cortisol with low doses oral dexamethasone
2. Loss of the normal circadian rhythm of cortisol with inappropriately elevated late-night serum or salivary
3. Increased 24-hour urine free cortisol (Carbamazepine and fenofibrate causes false elevation urine free cortisol)

Dexamethasone is used for suppression testing because it does not cross react in immunoassays for cortisol.

I. An overnight dexamethasone suppression test involves administration of 1 mg dexamethasone at 2300 hrs and measurement of serum cortisol at 0900 hrs the following day. Anti-seizure drugs (like phenytoin, phenobarbitone & primidione) and rifampicin accelerate the metabolism of dexamethasone causing a lack of cortisol suppression by dexamethasone.

II. In a low dose dexamethasone suppression test (LDDST) , serum cortisol is measured following administration of 0.5 mg dexamethasone 4 times daily for 48 hours. For eithers test, a normal response is a serum cortisol of < 50nmol/L (1.8ug/dL). In other wards if serum cortisol is > 50% of normal it is highly suggestive

cyclicity of cortisol secretion is a feature of all types of Cushing syndrome and, if very variable, can confuse diagnosis .Use of multiple salivary cortisol samples over weeks or months can be helpful in diagnosis but an elevated salivary cortisol alone should not be taken as proof of diagnosis .In iatrogenic Cushing syndrome cortisol levels are low unless the patient is taking a glucocorticoid **(such as prednisolone)** that cross reacts in immunoassays with cortisol.

Scanned with CamScanner

B. Determining the underlying cause

Once the presence of Cushing syndrome is confirmed, measurement of plasma ACTH is the key to establishing the differential diagnosis; it is the best measured in morning around 0900 hrs. In the presence of excess cortisol secretion, an undetectable ACTH (<1.1 pmol/L (5ng/L)) indicates an adrenal cause while ACTH level of >3.3 pmol/L (15ng/L) suggest a pituitary cause or ectopic ACTH. ACTH levels between these values represent a grey area and further evaluation by a specialist is required. Tests to discriminate pituitary from ectopic sources of ACTH rely on the fact that pituitary tumorous, but not ectopic tumours retain some features of normal regulation of ACTH secretion. Thus, a pituitary dependent Cushing disease, ACTH secretion is suppressed by high dose dexamethasone, and ACTH stimulated by corticotrophin-releasing hormone (CRH). In a high dose dexamethasone suppression test (HDDST), serum cortisol is measured before and after administration of **2 mg of dexamethasone 4 times** daily for 48 hours and if it is > 50% of normal it is highly suggestive of Cushing disease.

MRI detects around 60% of pituitary microadenomas secreting ACTH. If available, bilateral inferior petrosal sinus sampling (BIPSS) with measurement is ACTH is the best means of confirming Cushing disease, unless MRI shows a tumour bigger than 6 mm, in which case it may not be indicated. CT or MRI of adrenals detects most adrenal tumours and which is most often adrenal adenoma; adrenal carcinomas or usually large (>5cm) and have other features of malignancy including features of virilisation .for detection of ectopic source of ACTH , CT of chest & abdomen with particular attention to lung carcinoid , thymus and pancreas. If CT scan fails to identify the ectopic focus the next best step is whole-body-imaging with ^{68}Ga-somatostatin receptors –PET/CT (^{68}Ga-DOTATOTATE-PET/CT) (82% sensitivity) followed by whole body imaging with ^{18}F-DOPA-PET/CT (58% sensitivity).

What is insulin stress test? and what are its contraindications

It is also called insulin intolerance test and it is used to differentiate true Cushing syndrome and pseudo –Cushing syndrome

- In pseudo-cushing's the insulin tolerance test will demonstrate hypoglycaemia with a rise in ACTH and cortisol while in true cushing this hypoglycaemia response is lost
- Additionally , the hall mark of true cushing syndrome is lack of diurnal variation in serum cortisol while in pseudo-Cushing diurnal variation is normally maintained
- **Contraindications** of insulin stress are , epilepsy ,IHD and hypoadrenalism

How will you treat this patient?

Treatment depends upon the specific cause

i. **Pituitary Cushing Disease**

Treatment of choice is trans-sphenoidal surgery with selective removal of the adenoma. In experienced hand, the remission rate is 80-90% while rest of the patient suffer a recurrence, often

Scanned with CamScanner

years later, and therefore needs lifelong follow-up. In case, recurrence tumour is resectable then again trans-sphenoidal surgery is indicated and otherwise laparoscopic bilateral adrenalectomy is the best option .Additionally, residual or recurrent ACTH-secreting pituitary tumour may also be treated with stereotactic radiosurgery. Pituitary radiosurgery is also indicated for treatment of **nelson syndrome** (loss of negative feedback →↑ACTH → macro adenoma and ↑pigmentation) resulting from laparoscopic bilateral adrenalectomy of pituitary-dependent Cushing syndrome. The Somatostatin analogue, **Pasireotide** (↓ ACTH secretion from the tumour) is also licensed for the treatment of Cushing disease.

ii. **Benign adrenal adenoma**

Laparoscopic adrenal surgery is the treatment of choice for adrenal adenoma while patients with bilateral adrenal macronodular hyperplasia may require bilateral adrenalectomies and evaluation **for carney complex** (autosomal dominant condition characterized by endocrine glands tumours, spotty skin pigmentation, myxomas of the heart and facial freckles).

iii. **Adrenocortical carcinoma**

iv. It should be resected surgically and post –operative secondary adrenal insufficiency is a good prognostic sign while detectable postoperative cortisol level suggest metastases .Mitotane 0.5-1g BD (adrenalytic agent) is given postoperatively to secretory as well as non-secretary adrenocortical carcinoma for 2-5 years .However , it is associated with hypogonadism, hypothyroidism and primary adrenal insufficiency and therefore replacement hydrocortisone or prednisolone should be started when mitotane dose reach 2g daily .For **recurrent & metastatic** combined chemotherapy like etoposide ,doxorubicin ,cisplatin and mitotane (EDP-M). . 5-years survival rates of treated adrenocortical carcinoma correlated with ENSAT stage (stage 1→81%, stage2→61%, stage 3→50% and stage 4→13%)

v. **Ectopic ACTH-secreting tumours**

Localized tumours should be surgically resected if possible (like bronchial carcinoid) while if it is not resectable or metastatic we have the options of laparoscopic bilateral adrenalectomy and medical treatment with oral combination therapy like mitotane (3.5g/day), ketoconazole (0.4-1.2g/day) and metyrapone (3-4.5g/day).

vi. **Iatrogenic cushing syndrome**

It is treated with tapering dose of corticosteroid over weeks to months depending on the duration of steroid intake

vii. **Medical therapy and treatment of complications**

Medical therapy is indicated for patients who refuse surgery or when surgery is not successful or not indicated due to any reasons .the available drugs are mitotane, ketoconazole, metyrapone, cabergoline(0.5-3.5mg twice/weekly) and Pasireotide.

a. Hypertension (mineralocorticoid) can be treated with spironolactone, eplerenone and didyropyridine calcium channel blocker

Scanned with CamScanner

b. Symptoms of hyperandrogenism like hirsutism may be treated with flutamide(anti-androgens)
c. Treatment of osteoporosis with bisphosphonates
d. Following successful treatment of Cushing, syndrome secondary adrenal insufficiency occurs and requires long- term corticosteroid replacement. five years after successful surgery secondary hypoadrenalism resolves in about 58% of patients with pituitary Cushing disease 82% of those with ectopic ACTH and only 38% of those who had an adrenal tumour
e. Treatment of psychiatric issues

Recent advances in treatment of Cushing syndrome

Osilodrostat (↓ cortisol synthesis by blocking the adrenal enzyme 11B-hydroxylase) orally twice daily, can normalize urine free cortisol and improve the manifestation of hypercortisolism .Advere effects are adrenal insufficiency, ↑ adrenal testosterone synthesis, acne and enlarge pituitary tumour.

Prognosis

Following successful treatment (weather adrenal or pituitary) long-term prognosis are good and main cause of death is cardiovascular complications and bacterial infection.

Viva of adrenal insufficiency

It has variable presentation and therefore often-diagnosed late .it may present with weakness, abdominal pain, vomiting and diarrhoea .in primary adrenal insufficiency, weight loss is the uniform features. Sun-exposed area darkens the most but unexposed areas darken as well.

What are the causes of adrenal insufficiency?

Causes are mentioned below in the table while it is worth mentioning that worldwide most common cause is autoimmune disorder while in developing countries, the commonest cause is tuberculosis

How will you investigate this patient?

- **CBC** → Anemia, neutropenia, lymphocytosis and eosinophilia
- **Serum electrolyte** → low Na (88%) and high potassium (64%)
- **Fasting RBS**→ fasting hypoglycaemia is common
- **Serum Ca** → may be high
- **CT/MRI/X-ray adrenals** →adrenal calcification suggestive of TB while small no- calcified adrenal are seen in autoimmune Addison and enlarged adrenals may be due to metastatic and granulomatous disease
- **HIV serology**
- **Screening** for other autoimmune disorder like TFTs
- **Chest-X-ray→ old TB and small heart(microcardia)**

Scanned with CamScanner

Specific tests

- **Plasma cortisol** → < 3mcg/dL (83 nmol/L) at 8 AM is diagnostic if it is accompanied by elevated level of ACTH > 200pg/mL (44pmol/L). the diagnosis is confirmed by **short Synacthen Test** which is carried out as described below
- Synthetic ACTH (cosyntropin) 0.25 mg is given intramuscularly and serum cortisol is obtained 45 minutes after cosyntropin is administered. Normally serum cortisol rises to at least 20mcg/dl (550 pmol/l) whereas patients with adrenal insufficiency have stimulated serum cortisol levels less than 20 mcg/dl (550pmol/l). For patients receiving corticosteroids treatment hydrocortisone must not be given for at least 8 hours before the test while prednisone &dexamethasone do not interfere with specific assays for cortisol.
- cosyntropin may be administered during pregnancy, however the test may lack sensitivity since adrenal ACTH responsiveness increase during pregnancy
- serum **DHEA levels** are less than 1000 ng/ml (350 nmol/l) in patients with adrenal insufficiency but also in about 15% of the population so the test is very sensitive but not specific
- Serum **anti -adrenal antibodies** are found in about 50%of cases of autoimmune Addison disease the sensitivity of four serum anti-adrenal antibodies is as follows→ cytoplasmic antibodies (26%) 21 hydroxylase antibodies(21%) 17 hydroxylase antibodies (21%) and side chain cleavage antibodies (16%), additionally, antibodies to thyroid (45%) and other tissues may also be present
- Raised plasma **renin activity** (PRA) indicates the presence of depleted intravascular volume and the need for fludrocortisone administration serum epinephrine levels are low in untreated patients with adrenal insufficiency

How will you differentiate secondary adrenal insufficiency from primary?

In secondary adrenal insufficiency, ACTH and cortisol will be low while mineralocorticoid production is intact and therefore, there will be **normal potassium level** (instead of hyperkalaemia) and patients may **have normal to decreased skin pigmentation** called alabaster skin (instead of increased skin pigmentation in primary adrenal insufficiency).

Feature	Primary	Secondary
Site	Primary involvement of adrenal gland	Pituitary disease or prolonged use of steroid
Pigmentation	Present	Usually pallor
BP	Low	Normal
Electrolytes	Low Na+, high K+	Usually normal electrolytes
ACTH	High	Low

Scanned with CamScanner

Treatment

General measures

Patients and family members must be educated about adrenal insuffiency .Patients are advised to wear a medical alert bracelet.

Specific Therapy

Replacement therapy should include corticosteroids & mineralocorticoids for primary adrenal insuffiency. in mild cases corticosteroids alone may be adequate

- **Corticosteroid replacement therapy**

Maintenance therapy for most patients with Addison disease is 15-30 mg of hydrocortisone orally daily in two or three divided doses (e.g. 10 mg at 7 am 10 mg at 1 am and 5 mg at 7 pm). Some patients respond better to methylprednisolone in doses of about 3-6 mg daily in divided doses. Adjustments in dosage are made according to the clinical response. To determine the optimal corticosteroid replacement dosage, it is necessary to monitor patients carefully for clinical signs of over – or under replacement .A proper corticosteroid dose usually results in clinical improvement. .A white blood cell (WBC) count with a differential can be useful because a relative neutrophilia and lymphopenia may indicate corticosteroid over replacement and vice versa, however, serum ACTH levels vary substantially and should not be used to determine dosing.

The corticosteroid dose should be kept at the lowest levels at which the patients feels clinically well .Patients with partial ACTH deficiency (basal morning serum cortisol above 8 mg /dl {220 mmol/l } require hydrocortisone replacement in lower doses of about 5 mg orally twice daily or even 10 mg every morning. Some patients feel better with the substitution of prednisone (2-7.5) mg /day orally) or methylprednisolone (2-6mg/day orally) given in divided doses .Fludrocortisone is not required. Additional corticosteroid must be given during stress (eg infection trauma or surgical procedures) for mild illness or mild moderate surgical stress corticosteroid doses are doubled or tripled. For severe illness trauma or major surgical stress hydrocortisone 100 mg is given intravenously followed by 200 mg daily given as either a continuous intravenous infusion or as 50 mg boluses given every 6 hours intravenously or intramuscularly and then reduced to usual doses as the stress subside. Patients with secondary adrenal insuffiency due to treatment with corticosteroids require their usual daily dose of corticosteroid during minor surgery and mild illness while supplement hydrocortisone is required for majar surgeries or illness.

- **Mineralocorticoid replacement therapy**

fludrocortisone acetate in the dose of 0.05-0.3 mg orally daily or every other day in the presence of postural hypotension hyponatremia or hyper kalemia .If patient is intolerant of fludrocortisone acetate, alternative therapy is NaCl tablets to maintain normal serum sodium

- **DHEA replacement therapy DHEA**

Women with adrenal insuffiency, taking DHEA 50 mg orally each morning experienced an improved sense of well-being, increased muscle mass and a reversal in bone loss at the femoral neck. However, DHEA replacement does not improve fatigue cognitive problems or sexual dysfunction.

Scanned with CamScanner

- **Treatment of Acute Adrenal Crisis**

→ (In adrenal insufficiency, treat shortage of **4S** →salt (Na), Sugar (blood glucose), steroid and seui (Cantonese word which means→ water).

If acute adrenal crisis is suspected, intravenous access must be established blood is drawn for cultures, plasma ACTH, serum cortisol, serum glucose, BUN creatinine and electrolyte levels. A urinalysis is also done to screen for a urinary tract infection. Treatment is initiated immediately(without waiting for result) with hydrocortisone 100 mg by intravenous bolus followed by 50 mg intravenously every 6 hours as either intravenous boluses or a continuous intravenous infusion the hydrocortisone dosage may then be reduced according to the clinical scenario and laboratory result.

Intravenous fluids are administered as either 0.9% normal saline or 0.9% normal saline/5% dextrose solutions. Volumes of 2-3 L are infused quickly and then gradually reduce according to basic clinical parameters with frequent serum electrolytes and glucose determination. When intravenous saline is stopped, mineralocorticoid replacement is commenced with fludrocortisone, starting with 0.1 mg orally daily and adjusted according to serum electrolyte determinations.

Since **bacterial infection frequently** precipitates acute adrenal crisis, broad-spectrum antibiotics should be administered empirically while waiting for the results of initial cultures. The patient must also be treated for electrolyte abnormalities, hypoglycaemia, and dehydration, as indicated.

When the patient is able to take food by mouth, hydro- cortisone is administered orally in doses of 10-20 mg every 6 hours, and the dosage is reduced to maintenance levels as needed. Most patients ultimately require hydrocortisone twice daily (10-20 mg in the morning; 5-10 mg in the evening). Mineralocorticoid replacement is not needed when large amounts of hydrocortisone are given, but as its dose is reduced, it is usually necessary to add fludrocortisone acetate, 0.05-0.2 mg orally daily. Once the crisis is effectively treated, the patient must be evaluated to assess the degree of adrenal insufficiency and to establish the cause, if possible

What are the common causes (DDs) of generalized pigmentation?

Following are the common causes

- Addison disease
- Hemochromatosis
- Primary biliary cirrhosis
- Kala-azar
- Chronic renal failure
- Chronic arsenicosis
- Chronic illness like TB, malabsorption and cirrhosis of liver

What are the common causes (DDs) of skin pigmentation?

- Addison disease
- Hemochromatosis
- Primary biliary cirrhosis

Scanned with CamScanner

- Kala-azar
- Chronic renal failure
- Venous eczema
- Cafe-au-lait spots

What are the common causes (DDs) of buccal pigmentation?

- Addison disease
- Leukoplakia
- Melanoma
- Lichen planus
- Peutz-Jehger syndrome

What are the hypos /hypers of Addison disease?

Hypo

- Hypotension
- Hypoglycaemia
- Hyponatremia
- Hypo-PH(low PH)
- Hypo-cortisolism

Hyper

- Hyper-kalemia
- Hyper-renin

What is the unique feature of Addison disease in female?

- Loss of axillary and pubic hair is unique to female , because androgens are produced in females from the adrenal cortex
- In Addison disease hypotension is due to mineralocorticoid deficiency while postural hypotension is due to glucocorticoid deficiency as it is essential for vasomotor tone

What is autoimmune polyglandular syndrome (APS)?

Addison disease is associated with other endocrine deficiencies in approximately 10% of patients

There are two distinct types

Feature of autoimmune polyglandular syndrome (APS) type 1

Features (2 or more of the following)

- primary Hypoparathyroidism in 90%
- Addison's disease in 60%
- Chronic mucocutaneous **candidiasis** (typically **first** feature as young child)

Features of autoimmune polyglandular syndrome (APS) type 2

- Addison's disease plus either:
- Type 1 DM or
- Autoimmune thyroid disease

Scanned with CamScanner

(Hypothyroidism)

While vitiligo, myasthenia gravis, primary hypogonadism, celiac disease, and pernicious Anemia can occur in both types of APS.

- Usually TFTs are abnormal at the time of diagnosis of adrenal insufficiency (↑ TSH and ↓ T4)
- In-patient with hypoadrenalism and hypothyroidism, you cannot commence thyroid hormone replacement at this stage as it may precipitate a rapid deterioration in his adrenal crisis. Therefore, It would be most important to confirm the diagnosis of adrenal insufficiency by short-Synacthen test, then commence IV hydrocortisone then recheck the TFTS a few weeks later after stabilizing glucocorticoid replacement and if still hypothyroid then start thyroxine.

Scanned with CamScanner

APPROACH TO HEADACHE (Due to Acromegaly)

P/C **Headache** **3 months**

My patient presented with complaint of headache for the last 3 months. According to the patient, it was of gradual onset, continuous in nature, progressively worsening over time involving the whole the head .The intensity of headache is moderate, and patient 8/10 .it is stabbing in character and does not radiate to neck or any part of the body. It exacerbates with coughing and relived temporarily with painkiller medication, however, it reoccurs after sometime and stays throughout day and night. It is associated with decreased visual acuity, pain in the joints and increased sweating. However, there is no HX of …

Now exclude DDs of headache

a. **Stroke /SAH**→ there is no HX of weakness of any part of the body
b. **SOL**→ there is no HX of morning headache ,vomiting and focal neurological deficit
c. **Tension headache** →there is no HX of disturbed sleep and stress these days
d. **Cluster Headache**→ there is no HX of excruciating eye pain that is associated with redness of eye and nasal congestion
e. **Migraine** →there is no HX of unilateral pulsating headache associated with aura and nausea
f. **Giant Cell arteritis** – there is no HX of unilateral visual loss and scalp tenderness associated with headache
g. **Meningitis** →there is no HX of fever ,neck stiffness associated with headache
h. **HIV ,TB , Malaria** →there is no HX of high risk sexual behaviour , contact HX with a TB patient and recent travelling without taking malaria prophylaxis
i. **ENT infection** →there is no HX of recent flu , postnasal drip associated with headache
j. **Drug induced headache** →there is no HX of intake of CCB , nitrates and OCP
k. **Idiopathic intracranial hypertension** → there is no HX of eye deviation associated with headache
l. **Head trauma** →there is no HX of recent head trauma
m. **Cushing syndrome** →there is no HX of recent weight gain , easy brusibility ,excessive hair on body associated with headache
n. **Hyperthyroidism** →There is no HX of heat intolerance , tremors and weight loss associated with headache
o. **Acromegaly** → long case(see RECA)
p. **Pheochromocytoma**→ there is no HX of episodic sweating ,palpitation and tremors associated with headache
q. **Cervical Spondylosis**→ there is no HX of neck pain radiating to shoulders associated with headache

➢ **CARE of Acromegaly**

Complications of acromegaly

- Hypertension (50%)

Scanned with CamScanner

- Cardiomyopathy (10%)
- Colonic polyps and colorectal cancer
- Diabetes (30%)
- Pseudogout
- Hypopituitarism & pituitary apoplexy
- Carpel tunnel syndrome
- Obstructive sleep apnoea
- Cord compression due to arthritis of spine
- Thickened skin & ↑ sweating
- Myopathy
- Visceromegaly like ↑ liver

Examination (systemic review)

GPE→ Face → coarse facial appearance, enlargement of lips, nose and tongue, ↑ interdental spaces, prominent supraorbital ridges, prognathism and cutis verticis gyrate of scalp folds (due to expanding but tethered skin)

GPE→ Spadlike hands, carpel tunnel syndrome, enlargement of feet &↑ heel pad thickness, ↑ BP, thickened skin and excessive sweating, enlarged thyroid (20%) and acanthosis nigricans

Eyes →look for cataract, quadrantanopia (bitemporal hemianopia), visual acuity, and fundascopy

Breast → Gynenomastia

CVS→ cardiomyopathy, IHD, heart failure and arrhythmias

Abdomen →visceromegaly, Ca colon (do DRE→ for polyps and CA)

MSK→ Proximal myopathy and arthritis (Pseudogout), spinal stenosis

Now ask relevant

PAM-HUGS-FOSS-TV -F

Scanned with CamScanner

VIVA OF ACROMEGALY

How will you investigate this patient?

- **RBS** → Diabetes
- **LFTs & RFTs** →to exclude false elevation of growth hormone)
- **FT4 & TSH**→ to detect secondary hypothyroidism
- **Serum calcium** →for hyperparathyroidism as part of MEN-A
- **Colonoscopy**→ polyps and CA colon
- **ECHO**→ **cardiomyopathy**
- **Fundascopy**→ papilledema
- **Prolactin** → may be raised in 30% of the patients

Specific tests

- **For screening** →random serum insulin like growth factor -1 (IGF-1 and if it is within normal range it rule out acromegaly. However , if it is ↑ then we will proceed as follow
- Oral glucose tolerance test (OGTT)
- Conduct OGTT with baseline growth hormone (GH)→measure GH after 2 hours →if the GH is suppressed →acromegaly is rule out
- If GH is not suppressed (in 30% cases there is paradoxical rise) →it confirm the acromegaly
- (In normal patients GH is suppressed to < 2mu/L with hyperglycaemia and this is due to the fact that insulin and GH are antagonistic hormones)
- **Pituitary MRI** →it may show in >90% patients pituitary tumour(macro adenoma).However if it is normal despite high suspicion of acromegaly the next best step is to screen for an extra pituitary cause like CT scan of the chest and abdomen and measures GHRH.

Treatment

The main objectives of treatment is to improve symptoms and to normalise serum GH and IGF-1 to reduce morbidity and mortality .We have following options of treatment

a. Pituitary Microsurgery

Trans-sphenoidal surgery is the procedure of choice in the majority of the patients and achieves a remission about 70-80% of patients. it may be complicated by infection , leakage of CSF and hypopituitarism

b. Medications

- Somatostatin analogs like Octreotide & lanreotide

Octreotide LAR and lanreotide are long acting that are given by monthly subcutaneously .it is effective in 79% of patients (archives GH < 2ng/mL) and normalized IGF-1 in 53% of the patients.

- Dopamine agonist e.g. bromocriptine &cabergoline

Cabergoline is the oral agent of choice particularly in tumours that secrets prolactin along with GH .it will shrink one-third the tumours size in >50% cases .Additionally, it is safe in pregnancy .the initial dose is 0.25mg twice/weekly orally and then gradually increased to 1mg TDS/weekly

- GH receptor antagonists e .g pegvisomant

Scanned with CamScanner

Once daily s/c administration. It decrease lGF-1 levels in 63% of patients to normal .it is indicated when tumour is resistant to other treatment and particularly when there is associated diabetes .However, it

does not reduce tumour volume therefore surgery still needed if there is mass effect. The major use of pegvisomant is in patients who have an inadequate response to surgery or radiotherapy (is a third – line treatment when surgery radiotherapy and Somatostatin analogues are not effective

- **Selective estrogen receptor modulator(SERM) e.g. Raloxifene**

It is useful in acromegaly patients who are postmenopausal or who have had breast cancer. Raloxifene (60mg BD orally) does not reduce the GH levels, however, it normalize IGF-1 in 46% of patients

c. Stereotactic Radiosurgery

If acromegalic patients did not achieve a complete remission with above-mentioned options, then they may be treated with Stereotactic radiosurgery (like cyber knife, Gamma Knife and proton beam radiosurgery). Following pituitary radiation therapy, patient is advised to take lifelong low dose daily aspirin due to ↑ risk of stroke. Stereotactic radiosurgery of pituitary may cause hypopituitarism (in 35-60%) of the patients within 5 years; therefore, patient pituitary function should be regularly monitored.

Scanned with CamScanner

APPROACH TO HYPERTENSION

HTN may present with any of the following complaints

P/C Headache (already done in acromegaly), Altered sensorium & Uncontrolled B.P (see next)

HOPI (ODPARAV) of altered sensorium

My patient known case of HTN for the last 10-year presented with altered state of sensorium -5 days back .Describe the statement in standard pattern. Like sudden or gradual in onset, patient describes his symptoms as complete loss of consciousness or drowsiness but arousbale. There is /no HX of irritability, aggressive behaviour, irrelevant talk, mood disturbance, change in personality and memory .these symptoms persist for specific time or throughout day & night and associated (or not) with any involuntary purposeless movements of the body. There are no reliving or exacerbating factors.

DDs of Altered Sensorium

- **Trauma** →there is no HX of recent fall , head injury and RTA
- **Meningoencephalitis**→ no HX of fever , neck stiffness associated with altered sensorium
- **Stroke** →No HX of weakness of any part of the body
- **SOL** patient denied early morning headache that is exacerbated by straining and projectile vomiting
- **Cerebral malaria** →No HX of recent travel ,high grade fever associated with rigors & chills
- **DCLD**→ No HX of previous Hep B&C infection, blood in the vomiting and black tarry stool associated with altered sensorium
- **CKD**→ there is no HX of ↓ urine output , blood in the urine , sallow complexion and renal replacement therapy
- **CO2 retention** → there is no HX of biomass exposure ,whistling chest sound, shortness of breath and chronic use of inhaler
- **DM**→(Hypo & hyperglycaemia like DKA) there is no past HX of diabetes or HX of double vision ,shaking of body , abdominal pain associated with rapid shallow breathing
- **Sun-stroke** →there is no HX of working in hot weather and ↑ sweating associated with altered sensorium
- **Drug induced psychosis** →there is no HX of recreational drugs like amphetamine ,cocaine ,ice and alcohol
- **Myxoedema coma** →there is no HX of cold intolerance , low temperature and periorbital puffiness associated with altered consciousness
- **Addisonin crisis**→ there is no HX of darkening of skin , postural dizziness , abdominal pain and vomiting
- **Thyroid storm** →there is no HX of heat intolerance , palpitation , tremors associated with altered sensorium
- **Uncontrolled HTN**

Scanned with CamScanner

APPROACH TO UNCONTROLLED HYPERTENSION (Due to Pheochromocytoma)

P/C

Uncontrolled B.P 2 days

My patient who is known case of HTN for the last 10 years presented with complaint of uncontrolled BP .According to the patient he has severe headache 5- day back for which he checked his blood pressure which was quite high (220/120) and he went to a local doctor where he gave him blood lowering medication but his BP reading were still high. Therefore, the doctor started him on intravenous medication, however, his blood pressure remained high and the doctor advised him to visit the tertiary care hospital. According to the patient, he was complaint to the medication and dietary modification and he was not under stress these days. The headache was associated with palpitation, sweating and tremors of his hands; however, patient denied, severe left-sided chest pain, weakness of any part of the body and decreased urine output.

History dates back about 10 year ago and at the age of (mentioned less than 35-years), he had persistent headache, and therefore, visited to local GP where his BP was raised .Therefore, the doctor advised him life- style modification and on follow –up visits his blood pressure was still high and consequently the doctor advised him BP lowering medication and advised investigations which were refused by the patient. However, according to the patient he had good compliance to medication and dietary modification like taking low salt diet. However, the patient denied

DDs

- **Primary HTN**→ ask about atherosclerosis risk factor like sedentary life style , dyslipedemia , active smoking and family HX of HTN

Secondary Causes of HTN (always exclude in patient age < 40 years)

I. **Endocrine causes**

- **Acromegaly**→ no HX of change in the size of shoes and facial appearance
- **Cushing syndrome** →no HX of weight gain , easy brusibility and excessive hair on the body
- **Hyperthyroidism**→ no HX of heat intolerance , weight loss and tremors
- **Hypothyroidism** →no HX of weight gain , cold intolerance and dryness of skin
- **Hyperparathyroidism**→ no HX of abdominal and flank pain , constipation and psychiatric disturbance
- **Primary hyperaldosteronism(Conn's) syndrome** → No HX of muscle weakness& cramps , easy fatigability and abnormal electrolyte level
- **Pheochromocytoma**→ there is HX of labile HTN, episodic pallor of complexion, palpitation, sweating & headache and diagnosis of mass in the abdomen.
- **Congenital adrenal hyperplasia (due to 11-beta –hydroxylase or 17-alpha –hydroxylase deficiency**) →there is no HX acne , rapid growth during childhood and excessive body hair
- **Liddle's syndrome**→ same presentation as Conn's syndrome (but low renin and aldosterone level).

Scanned with CamScanner

II. **Renal causes**

- **Parenchymal renal disease Particularly GNs** →there is no HX of periorbital puffiness , decreased urine output and blood in the urine
- **Renal vascular disease like stenosis or arteriosclerosis** → there is no HX of unequal size-kidney on ultrasound
- **APCKD** →No HX of abdominal mass or multiple cysts in kidneys on ultrasonography
- **Chronic pyelonephritis** →No HX of shrunken kidneys on ultrasonography
- **CKD(may be a cause or complication of HTN)** →there is no HX of pedal edema , sallow complexion and renal replacement therapy

III. **Cardiovascular causes**

- **Coaractation of the aorta** →no HX of unequal BP in both arms and notching of ribs on x-ray
- **Obstructive Sleep apnoea**→ No HX snoring , disturbed night sleep and obesity
- **Obesity** →the patient is not over-weight or obese

IV. **Rheumatological causes**

- **PAN**→ there is no HX of joints pain , weight loss , abdominal pain , blood in the urine and testicular pain
- **Takayasu arteritis** →No HX of difference in blood pressure between arms and pain in calves on walking (claudication due to PAD) and absent of pulse in the arm
- **Systemic sclerosis** →there is no HX of tightening of the skin, epigastric burning sensation and difficulty in swallowing.
- **SLE** →No HX of oral ulcer , photosensitivity and hair fall

V. Drugs Induced HTN

Ask about certain drugs like nonsteroidal anti-inflammatory drugs corticosteroids, Calcineurin inhibitors, stimulants decongestants, tyrosine kinase inhibiters, estrogen, erythropoietin, alcohol, cocaine, gemcitabine, atypical antipsychotics and monoamine oxidase inhibitors

VI. Pregnancy

- Eclampsia and pre-eclampsia

VII. Alcohol

- Alcohol excess is one of the reversible cause of HTN

VIII. White Coat Hypertension

➢ **CARE of Pheochromocytoma**

Complications of HTN

- IHD,LVF,arrhythmias and sudden cardiac death
- Stroke /TIA and dementia
- Aortic dissection →sudden severe penetrating chest pain radiating to back associated with high BP
- AKI&CKD

Scanned with CamScanner

- PAD
- Retinopathy
- Hypertensive urgency and emergency →HX of emergency visit to hospital due to very high BP with or without associated end organ damaged
- Ask about complication due to anti-hypertensive drugs like dry cough & angioedema (ACES), ankle edema (CCB), exacerbation of airway disease (BB) and gout and ↑urination (Diuretic).

Now ask relevant

FAM-HUGS-FOSS-TV

Examination

Scanned with CamScanner

VIVA OF HYPERTENSION

How will you investigate this patient?

- CBC→ Polycythaemia
- RFTs→
- LFTs→ Alcoholic liver disease
- Serum electrolyte → ↓ K may indicate various endocrine causes of hypertension(see below)
- Blood glucose &HbA1c
- Serum total and HDL cholesterol
- Urine R/E for blood ,protein and glucose
- ECG & ECHO
- Fundascopy
- Chest-Xary →Coaractation of aorta , heart failure and cardiomegaly
- Ambulatory BP recording to assess borderline or white coat hypertension

Special investigations

- **TFTs**
- **Renal ultrasound** →Renal parenchymal & renovascular disease
- **Renal angiography** → to detect or confirm the presence of renal artery disease
- **24-hour urinary cortisol and dexamethasone suppression test** → Cushing syndrome
- **Plasma renin and aldosterone** → to detect primary aldosterone
- **IGF-1 and OGTT**→ acromegaly
- **ENA profile** → auto immune disorders like SLE ,RA, and systemic sclerosis
- **Serum Ca & phosphate , PTH**→ Hyperparathyroidism
- **Sleep studies** →**OSA**
- **24 hours catecholamine (& VMA) ,CT adrenal**→ Pheochromocytoma
- **Plasma aldosterone and renin ratio**→ primary aldosterone
- **Ultrasound** →APCKD and renovascular disease
- **Urine toxicology screening** → for ecstasy drugs
- **Trans-thoracic Echocardiography** →Coaractation of aorta

What are the stages of hypertensive retinopathy?

Grade 1	Grade 2	Grade 3	Grade 4
* Arteriolar thickening, tortuosity and increased reflectiveness ('silver wiring')	Grade 1 plus constriction of veins at arterial crossings ('arteriovenous nipping')	* Grade 2 plus evidence of retinal ischemia (flame-shaped or blot haemorrhages and 'cotton wool' exudates)	* Grade 3 plus papilledema

Name few guidelines that are commonly used for hypertension

- NICE guideline

Scanned with CamScanner

- American Heart Association (AHA)
- European society of cardiology (ESOC)
- Joint National Committee on Detection , Evaluation and Treatment of High Blood Pressure(JNC-8)

What is the NICE classification of hypertension?

HTN stages Clinic BP ABPM or HBPM

- Stage 1 → 140/90 135/85
- Stage 2 → 160/100 150/95
- Stage 3→ 180/120 does not require ABPM /HBPM

While JNC-8 classification is

- Stage 1→ 140-159/80-89
- Stage 2→ ≥160/100

➢ Target BP according to JNC-8 is < 140/90 while in CKD or diabetes target BP is less than 130/80.

Optimal target of BP according to NICE guideline		
Age	Clinic BP (mmHg	Ambulatory or home BP (mmHg)
1)→< 80 years	< 140/90	< 135/85
2) →≥ 80 years	< 150/90	< 140/85

As we already know, NICE ACD (ACEs, CCB and diuretics) protocol for hypertensive patient without premorbid for age less than 55 and more than 55 years so there is no point discussing this in detail here.

What do you know about impact of lifestyle modification on hypertension?

Modification	Intervention	Resulting ↓↓ in Blood Pressure
Weight loss	Target BMI 18.5-24.9	5-20 mm Hg/ 10-kg loss
DASH diet	Fruit, vegetables, low fat dairy	8-14 mm Hg
Sodium intake	.< 100 mmol/day (<6 g salt)	2-8 mm Hg
Alcohol intake	Male ≤ 2 drinks/day Female ≤ 1 drink/day	4 mm Hg
Exercise	Aerobic 30 min/day Dynamic 90-150 min/week Isometric (hand grip 4 repetitions 3 times/week)	5-10 mm Hg
Mindfulness	Meditation and breathing control	5 mm Hg

- **American Heart Association (AHA)** → a target BP of less than 130/80 mmHg is recommended for adults with confirmed hypertension and CVD or a 10- year CV risk of ≥10%.

Scanned with CamScanner

- **European society of cardiology (ESOC)→** recommends treated BP values to a range of 120-129/<80 mmHg and 130-139/<80 mmHg in patients less than 65 years and those aged ≥ 65 years, respectively .

Comparison of blood pressure treatment thresholds of different guidelines.

Guidelines	Cardiovascular Risk	Threshold for Pharmacotherapy (mm Hg	Target (mm Hg)
ACC/AHA	Not increased	> 140/90	<130/80 (reasonable)
Hypertension Canada	Not increased	160/100>	< 140/90 (<130/80 for diabetes)
ESH/ESC	Not increased	> 140/90	All < 140/90, most < 130/80, not < 120
ACC/AHA	Increased	< 130/80	<130/80
Hypertension Canada	Increased	> 140 systolic	< 120 systolic
ESH/ESC	Increased	> 130/80	120-130/<80
ACC/AHA > 65 year	Risk due to advanced age	> 130/80	< 130 systolic
Hypertension Canada	Increased	Not specified For age > 75	Not specified For age >75 year
ACC/AHA > 65 year	Not increased	> 140/905	130-140/> 80

What is resist[illegible] ypertension?

Resistant hypertension is defined as the failure to reach blood pressure control in-patient who are adherent to maximum tolerated of an appropriate three-drug regimen (including a diuretic).

Causes of resistant HTN

➢ What is hypertensive urgency & emergency?

In hypertensive, urgency BP is is raised (> 180/120) without end orange damaged while in hypertensive emergency raised BP is associated with an end organs damaged. Emergencies include hypertensive encephalopathy (headache irritability confusion and altered mental status due cerebrovascular spasm), hypertensive nephropathy (haematuria proteinuria and acute kidney injury due to arteriolar necrosis and intimal hyperplasia of the interlobular arteries), intracranial haemorrhage, aortic dissection, preeclampsia, eclampsia, pulmonary edema, unstable angina or myocardial infarction.

Encephalopathy or nephropathy accompanying hypertensive retinopathy (Papilledema) is called **malignant hypertension** but the therapeutic approach is same to that used in other hypertensive emergencies.

Management of hypertensive emergency include parenteral therapy, particularly if encephalopathy is present .the initial goal is 25% reduction of blood pressure within 1-2 hours that is followed by gradual reduction of BP toward a level of 160/100 mmHg within 2-6 hours .rapid lowering of BP may precipitate coronary , cerebral or renal ischemia

Scanned with CamScanner

- **Acute ischemic stroke**→ anti-hypertensive medication is only indicated if BP is ≥180 and should be reduced only 10-15% very cautiously. It is recommended to keep BP <185/110 during and for 24 hours if thrombolytic therapy is indicated.
- **Intracerbral haemorrhage**→ it is advised to lower & maintain BP to 130-140 mmHg within the first 6 hours to ↓ bleeding. While in case of acute subarachnoid haemorrhage, until the bleeding source remains uncorrected, it is recommended to maintained adequate cerebral perfusion in the face of cerebral vasospasm while measures must be taken to prevent further bleeding and maintaining adequate cerebral perfusion in the face of cerebral vasospasm. In this situation, blood pressure goals depend on the patient's usual blood pressure. In previously normotensive patients, the target should be a systolic blood pressure of 110-120 mm Hg , while in hypertensive patients, blood pressure should be treated to 20% below baseline pressure. Patients **with subarachnoid haemorrhage** should receive nimodipine (60mg QID) for 3 weeks to minimize cerebral vasospasm. In hypertensive emergencies due to catecholaminergic aetiology, such as **Pheochromocytoma** or cocaine use, beta-blockers can worsen the hypertension because of unopposed peripheral vasoconstriction; and therefore nicardipine, clevidipine, or phentolamine is preferred. Labetalol is useful in these patients if the heart rate must be controlled. ACE inhibitors are specifically indicated for hypertensive crisis from systemic sclerosis (**scleroderma**). In acute aortic dissection, systolic blood pressure and heart rate should be reduced within 30 minutes to below 120 mm Hg and less than 60 beats per minute, using a combination of vasodilation and beta-blockade.
- **Treatment of hypertension in Diabetes**→ most guidelines suggest target BP less than 130/80 mmHg and due to beneficial effect of ACE inhibitors in diabetic nephropathy, therefore, it should be included in the treatment.

➢ **Pregnancy Induced Hypertension** → BP ≥140/90 before 20 weeks of gestation

➢ **Pre-eclampsia**→ BP≥ 140/90 mmHg after 20 weeks of gestation

➢ **Eclampsia** → pre-eclampsia and fits is called eclampsia.

Recent advances→ FDA approved in 2024 **aprocitentan** (12.5mg PO qDay) (endothelin antagonists) for treatment of resistant hypertension.

Scanned with CamScanner

APPROACH TO JOINTS PAIN (RA & SLE)

P/C

Worsening of joints pain since 1 month

ODPARAV (HOPI)

My patient who is normotensive and normoglycemic presented with worsening of joints pain (small joints of hands) that is gradual in onset, one month in duration and progressive in nature .According to the patient , the pain initially started as symmetrical /asymmetrical involvement of these joints (mention affected joints of upper or lower limbs) that was mild to moderate in intensity along(mention pain score out of 10) with associated restriction of movement as described by patient, unable to performed daily activities like house chores . Pain is more prominent in morning that persists throughout the day, ↓ with activity and partially relived with painkiller medication and reoccur after sometime .pain is associated with morning stiffness that last almost for 1 hour and improve with activities and joint swelling (or mention SLE features like photosensitivity, hair fall, mouth ulcer etc) .However, there is no associated HX of joint deformity, joint redness and low grade fever. However, there is no HX of…

Exclude DDs of joints pain

- **RA** →there is no HX of previous joint deformity and taking of weekly basis medication for treatment of joint pain
- **SLE**→ there is no HX of oral ulcer , skin rash , photosensitivity and HX of recurrent abortion in 1st trimester
- **Systemic sclerosis** →there is no HX of tightening of skin and difficulty in swallowing
- **Sjogren syndrome** →there is no HX of dryness of eyes , oral cavity and parotid enlargement
- **Psoriasis**→ HX of silver scaly rash on the skin
- **Dermatomyositis & polymyositis** →there is no HX of painful muscles ,skin rash involving eyelids &dorsum of the hands and difficulty of standing from sitting position
- **Ankylosing spondylitis** → HX of low back and stiffness in the morning
- **IBD**→ there is no HX of diarrhoea with blood in the stool
- **Reactive arthritis** →HX of redness of eyes following genital , urinary infection or loss stool
- **Behcets Disease**→ HX of recurrent oral , genital ulceration or infection
- **Gout** →HX of recurrent big toe swelling following ↑ intake of protein diet and raised uric acid level .
- **Vasculitis** →HX of palpable skin rash , abdominal pain and blood in urine or sputum
- **Sarcoidosis** →HX of SOB , dry cough and painful skin nodules on shin
- **Chronic Viral infection (HBV,HCV&HIV)**→ HX of surgery , blood transfusion and high risk sexual behaviour
- **Malignancy** → HX of ↓ appetite , Lumps &bumps in the body and weight loss
- **Hemochromatosis**→ there is no HX of DM , erectile dysfunction and skin discoloration
- **Rheumatic fever** →there is no HX of throat infection ,migratory joint pain and skin nodules

Scanned with CamScanner

- **Adult-onset still disease**→ there is no HX of high grade fever associated with Salmon-pink maculopapular rash and joints pain
- **Whipple disease** →there is no HX of chronic diarrhoea associated with memory loss , slow heart beat and joints pain
- **Osteomalacia** →there is no HX of ↓ intake of milk , vit D and muscle cramps

CARE (systemic review)

- **CNS** → ask about fits , depression, altered sensorium , neck pain on movements (in RA it may signify → subluxation) and numbness of hands& feet, carpel tunnel syndrome , mononeuritis multiplex
- **Eyes** → dryness and redness and ↓ visual acuity
- **RESP**→ SOB , blood in the sputum and dry or productive cough(ILD & bronchiectasis)
- **CVS**→ palpitation , SOB on exertion , orthopnoea and HX of IHD
- **GIT**→ difficulty in swallowing, jaundice, epigastric pain , retrosternal burning pain ,blood in the vomiting and black tarry stool (NSAIDS & steroid induced gastritis/PUD) and left hypochondrial heaviness(felty syndrome)
- **Renal** → periorbital puffiness , ↓ urine output and blood in the urine
- **SKIN**→ rash & nodules , tightening , nodules and pyoderma gangrenosum
- **Blood** →paleness of complexion , easy brusibility and recurrent infection(pancytopenia may be due to drugs or disease)
- **APLA(ant phospholipid)** → recurrent loss of pregnancy , use of blood thinning medications and swelling of unilateral limb
- **Associated autoimmune disorders** like thyroid & DM etc
- Ask about complication of medicine
- **Ask about** menstrual HX **in** and for pregnancy future plans (as patient may needs cyclophosphamide in some point in her life and therefore she may want to preserve her ova etc if her family is not completed yet) and contraception
- **Function status** → how much professional and daily activities has been affected by the illness

Ask about **ITP** (investigation, procedure like renal biopsy and treatment) and relevant **FAM-HUGS –FOSS-TV**

Standard Rheumatological examination (for short case and long case)

Examination of Hands:

- It consists of four steps i.e; **LOOK, FEEL ,MOVE & SPECIAL TESTS**
- Before starting the examination, ask patient to up roll their sleeves up to elbows and place the hands of patient on a pillow.

1. INSPECTION:

Dorsal Surface:

- Inspect DIPs, PIPs, MCPS, wrists for
- any swollen erythematous joints (if present remember the hand and finger) ,

Scanned with CamScanner

- Tappering of fingers (sclerodactyly)
- deformities (swan neck, button hole , Z deformity , ulnar deviation, subluxation at MCPs, dinner fork deformity at wrists) ,
- nodes (Herberdon nodes at DIPs, Bouchard nodes at PIPs)
- Rash overlying joints (PIPs, MCPs) (Gottron's papules)
- Wasting of dorsal interrossei muscles
- Nails (nail ridges and pitting, Onycholysis to rule out psoriatic nails) , periungal erythema ( ), splinter hemorrhages (Infective endocarditis in setting of SLE) , clubbing (in setting of RA related ILD)

Palmar Surface:

Inspect for

- fissuring rash (mechanic's hands suggestive of anti-synthetase antibody syndrome)
- hypothenar and thenar wasting ,
- Palmar erythema , Dupuytren's contractures
- scar at wrist may show previous surgery done for Carpal tunnel syndrome ,
- Finger tips for gangrene (dry or wet) , ulcers , pitting (shows old healed ulcers) , active Raynaud's phenomenon ,

Ask the patient to flex their elbows and examine extensor surfaces for Rheumatoid nodules and psoriatic patches

Palpation:

2. Palpation

Dorsal Surface:

- Ask patient if they have pain in any joints
- Start palpation by comparing temperature above and below the wrists
- Assess for tenderness of joints , start from wrists (examine with both thumbs) followed by MCPs, PIPs , DIPs (four fingers method)
- Assess for skin thickening (difficult to pinch in Scleroderma) , paper thin skin (Cushing's Syndrome)

PALMAR SURFACE:

Palpate radial pulses bilaterally (assess for radio-radial delay, rate, rhythm (conduction blocks are common in RA)

3. Movements:

Active Movements:

- Ask patient to perform adduction , abduction , opposition of fingers
- Extension and flexion at wrist joint

Movements against resistance:

- Examine for opposition, abduction of fingers against resistance applied by examiner's fingers

Scanned with CamScanner

- Examine for adduction of fingers against resistance by placing card between fingers
- Examine for pincer grip and hand grip
- Examine for wrist extension & flexion against resistance

4. SPECIAL TESTS :

- **Prayer sign** : Patients with deformities secondary to RA or diabetic Cheiroarthropathy may not be able to perform it
- **Reverse Prayer or Phalen's sign:**

Ask patient to hold their arms for 30-60 seconds in front of them with wrists flexed pointing downwards; if patient feels tingling sensation along distribution of median nerve, Phalen's test is said to be positive

- **Tinel's sign**: Tap with finger on flexor retinaculum
- **Functional capacity** : ask the patient to unbutton his shirt's button or give key to the patient and ask him to act as if he is trying to unlock the lock (Key in a lock test)

Relevant examination:

If deformities are suggestive of RA, in relevant examination look for signs of

- red eyes(episcleritis),
- ascultate bases of chest for ILD and heart for conduction abnormalities & murmurs
- Examine abdomen for splenomegaly (Felty's syndrome) ,
- Look for pedal edema (amyloidosis)
- Look for hidden psoriatic patches behind the ears, on scalp, umbilicus, and knees if DIP involvement is observed during examination.

In case of suspected SLE

- look for signs of alopecia (scarring / patchy) ,
- Face for malar or discoid rash , oral ulcers (palatal ulcers are more specific for SLE) ,
- Cushingoid features (iatrogenic) , proximal myopathy
- Ascultate for pleural effusion and pericardial effusion (serositis)
- Examine abdomen for organomegaly
- Look for pitting pedal edema
- Communicate with patient to assess orientation and examine cranial nerves (to rule our neuro-psychiatric SLE)
- Fundascopy (for optic neuritis, hypertensive retinopathy)

LONG CASE SCHEME OF RHEUMATOLOGY CASE:

Since most of the patients of rheumatology have arthritis and arthralgias (irrespective of the diagnosis), and if patient gives history of arthritis,

After vitals and GPE, examination should start with **musculoskeletal system**

- Start with the affected joints (e.g hands in case of RA, knees or ankles in case of AS)

Scanned with CamScanner

and then move on the hands (if they were not examined first) followed by wrists, elbows ,shoulders

- Then ask patient to lye down and examine hips, knees, ankles
- (Check swelling ,tenderness,deformities,contractures, Range of motion/movements in all joints in a systemic way)
- Gait should be examined too along with back examination (mentioned in Scheme of back examination) if patient has history suggestive of AS (Inflammatory lower backache with early morning stiffness)
- After completing musculoskeletal examination, proceed as per other complaints of patient.
- Skin findings should not be missed
- All systems, however should be examined as Rheumatological diseases can manifest with multi-systemic involvement
- CNS: Tone, power, reflexes, plantars, sensations , cranial neuropathies (rule out CVA , demyelinating disorders, neuropathies)
- CVS : examine for conduction blocks, murmurs , loud P2
- Chest : apical fibrosis (AS), ILD (RA, Scleroderma) , Pleural effusion (SLE serositis)
- Abdomen: visceromegaly , gut motility , aortic aneurysms (vasculitis)

Complete with fundascopy:

- Look for uveitis, Iris nodules (RA) ,
- pale disc (optic neuritis in SLE associated NMOSD, MOGSD) ,
- flame shaped hemorrhages and cotton wool spots (lupus nephritis, scleroderma renal crisis)

Scanned with CamScanner

VIVA of RA

How will you investigate this patient?

- **CBC** → pancytopenia
- **ESR &CRP**→ may be raised proportional to disease activity
- **RA factor** →RA factor has 50-70% sensitive and less specific .it may also be positive in in chronic HCV infection , Tuberculosis, syphilis and many other condition
- **Anti-CCP**→ it is highly specific for RA (> 95%)
- **ANA** → 20% of RA patients are positive for ANA
- **ENA profile** → to look for MCTD
- **X-ray hands, wrist and feet** →the earliest changes in the hands and feet are soft tissue swelling and juxt-articular demineralization (osteopenia) while late diagnostic changes are erosions and joint space narrowing. These radiographic changes are the most specific for RA.
- **MRI**→ Cervical spine with C1-2 subluxation but these changes takes years to develop
- **Chest-xary** →to exclude active or latent TB
- **LFTs**→ to check before DMARD
- **RFT** → to adjust dose accordingly
- **Urinalysis** → haematuria & proteinuria
- **Dexa –scan** →osteoporosis

What is the criterion for the diagnosis of RA?

- Patients with score ≥ 6 are considered to have definite RA

ACR Criteria For Diagnosis Of RA	
Criterion	Score
Joints affected 1 large joint→ 0 2-10 large joints→ 1 1-3 small joints→ 2 4-10 small joints → 3 > 10 joints (at least 1 small joint) → 5	
Serology Negative RF and ACPA → 0 Low positive RF or ACPA→ 2 High positive RF or ACPA → 3	
Duration of symptoms <6 weeks → 0 >6 weeks → 1	
Acute phase reactants Normal CRP and ESR → 0 Abnormal CRP or ESR→ 1	

Scanned with CamScanner

What are the markers poor prognoses of RA?

- Positive Anti-CCP antibodies (the poorest prognostic factors)
- HLA-DR4
- RA positive
- Extra articular features like nodules
- Poor functional status
- Female gender
- Insidious onset
- Early articular changes on x-ray (within 6 months of presentation and in less than < 2 years)

What are the extra- articular features of RA?

What are the extra- articular features of RA?

i. **Ocular**

- Keratoconjunctivitis sicca (the most common) , also called dry eyes and it is due to secondary sjogren syndrome
- Episcleritis(redness only)
- Scleritis(pain & redness)
- Ulcerative keratitis
- Steroid induced cataract(Posterior sub capsular)
- Chloroquine retinopathy

ii. **Cardiac**

- Constrictive pericarditis (most common)
- Heart block & aortic regurgitation
- Cardiomyopathy
- IHD

iii. **Pulmonary involvement**

- Pulmonary fibrosis
- Effusion (↓ low glucose level)
- Nodules
- Caplan's syndrome
- Pleurisy
- Cricoaryteniod arthritis (diagnosed with spirometery with flow-volume loop)

iv. **osteoporosis**

v. **Neurological**

- Spinal cord compression
- Mononeuritis multiplex
- Peripheral neuropathy
- entrapment neuropathies like bilateral carpel tunnel syndrome and other neuropathies

vi. **Felty syndrome** (RA+ splenomegaly and low white cell count)

vii. **Secondary amyloidosis**

Scanned with CamScanner

How will you treat this patient?

Treatment involves combination of pharmacological and non –pharmacological measures with objective of reduction of pain & inflammation, preservation of function and prevention of deformity.

❖ *Pharmacological therapy*

i. **Corticosteroid**

It is used as bridge therapy to control symptoms until the DMARDs takes effect and may also be use(**in higher doses**) to manage serious extra-articular manifestation like pericarditis, vasculitis, ILD and necrotizing scleritis. No more than 10mg of prednisolone or equivalent (or equivalent dose)/day is indicated for articular disease, however, high dose is indicated for serious extra-articular manifestation as mention above .Additionally, steroid may be used intra-particularly (Triamcinolone10-40mg) if one –two joints are affected. Patients who are on long term steroids should take measures to prevent osteoporosis

ii. **Synthetic Disease –modifying antirheumatic drugs (DMARDs)**

- **Methotrexate(MTX)** →it is the DMARD of choice
  - **MOA** →it inhibit dihydrofolate reductase, preventing the reduction of dihydrobiopterin (BH2) to tetrahydrobiopterin (BH4) leading to nitric oxidase synthase uncoupling and increased sensitivity of T cells to apoptosis, thereby diminishing immune response. (In short, MTX is purine synthesis inhibitor).
  - The initial dose is 7.5-10mg once weekly and max dose is 20mg/weekly
  - All the patient should be co-prescribed folic acid weekly 24-48 hours apart from methotrexate to ↓ gastric irritation, myelosuppression and hepatotoxicity
  - The most frequent adverse effect is gastric irritation and stomatitis while other serious effects are myelosuppression , hepatic fibrosis and cirrhosis , B-cell lymphoma and interstitial pneumonitis (it is an indication to **stop** the MTX)
  - MTX is contraindicated in pregnancy(Stop MTX 3-6 before trying to conceive) , chronic hepatitis and when GFR is < 30mL/min
  - Monitoring of CBC& LFTs (at least 12 weekly) is essential due to the risk of myelosuppression and hepatotoxicity (If ALT is raised then ↓ the dose of MTX and if ALT is still raised then stop MTX).
- **Sulfasalazine**
  - It is second –line agent for RA and it is usually prescribed 500mg BD with gradual ↑ dose of 500mg/week with max 3g/day.
  - **MOA** → it breakdown into active metabolite like sulfapyridine and 5-aminosalicyclic acid (5-ASA).the beneficial effect are predominately from anti-inflammatory properties of 5-ASA, which inhibits leukotriene synthesis and lipooxygenase. (In short MOA is prostaglandin synthesis inhibitor).
  - It adverse effects include neutropenia and thrombocytopenia (therefore, CBC should be monitored every 2-4 weeks for first 3 months and then every 3 months) haemolysis in G6PD deficient patients.

Scanned with CamScanner

- **Leflunomide**
- MOA →pyrimidine synthesis
- It dose is 20mg/day and should be stopped atleast 2 years before conception as it is teratogenic. It adverse effects include HTN , hepatotoxicity, reversible alopecia and weight loss
- **Hydroxychloroquine**
- It is use in combination with other DMARD and it dose is 200mg BD. The most important adverse effect is duration based retinopathy(occurring in less than 2% during the first 10 years and 20% after 20 –years) while other notable effects are neuropathies and myopathies

Recommended DMARD Blood Monitoring Schedule when starting or Adding a New DMARD

- Check CBC, creatinine/calculated GFR, ALT and/or AST and albumin
- Every 2 weeks until on stable dose for 6 weeks, then once on stable dose, monthly for 3 months and thereafter, at least every 12 weeks.

Contact rheumatology specialist urgently and consider interruption in treatment if any of the following develop:

- white cell count < 3.5 * 10 ^ 9 /|
- mean cell volume > 105fL
- neutrophils <1.6 × 10⁹/1;
- creatinine increase > 30% over 12 months and/or calculated GFR < 60ml / min
- unexplained eosinophilia > 0.5 * 10 ^ 9 / l ;
- ALT and/or AST >100 U/l;
- platelet count < 140 * 10 ^ 9 /|:
- unexplained reduction in albumin <30 g/l
- In the setting of acute-infection, most DMARDs except hydroxychloroquine) should be discontinued until the infectious process has resolved

iii. **Janus Kinase inhibitors**

- It includes **Tofacitinib**(5mg BD), **baricitanib**(2-4mg/day) and **updacitinib**(15mg/day) and it is indicated when RA is refractory to MTX and other agents .it is use either in combination with other agents like MTX or alone ,however , latent TB should be excluded or treated before initiating this therapy .

iv. **Biologic DMARDs**

1. **Tumor Necrosis Factor inhibitors (TNF –inhibitor)**

There are 5 TNF-inhibitor FDA approved for RA treatment and most of them are well tolerated and produce significant improvement in the disease activity. The adverse effect are irritation at injection sites, ↑ risk of serious bacterial infection particularly reactivation of latent TB, demyelinating neurologic complications that mimics MS and may ↑ mortality in heart failure patients.

- **Infliximab**→ it is monoclonal antibody and administered intravenously 10mg/kg followed by repeated infusion at 2, 6, 10 and 14 weeks and then every 8 weeks.
- **Etanercept** → 50mg subcutaneously / week

Scanned with CamScanner

- **Adalimumab** →40mg subcutaneously every other week
- **Golimumab** →50mg subcutaneously **/month**
- **Certolizumab** →200-400mg subcutaneously every 2-4 weeks
- **Contraindication of TNF –inhibitors**
- Pregnancy
- Active infection like TB
- Heart failure (NYHA3-4)
- MS

2. Rituximab (anti-CD20)

If the RA is refractory to anti-TNF agents then rituximab may be used in combination with synesthetic DMARDs. 1000mg IV infusion repeat after 2 week (2 infusion separated by 2 week is one course) while 375mg/m^2 iv monthly is the dose for Wagner .

3. ABATACEPT(CTLA4 inhibitor)

It inhibits T lymphocyte activation and indicated when RA does not respond to anti-TNF agents. It dose depends upon body weight like for < 60kg, 500mg , 60-100kg 750mg and >100kg→1000mg IV infusion is indicated and then above dose is repeated 2 weekly for two times followed by 4 weekly.

4. Tocilizumab and Sarilumab (IL-6 Receptor inhibitor)

Again it is indicated when RA is refractory to other therapy. It dose is 4-8mg/kg IV 4 weeks while SC dose is 162mg SC every other weeks (for < 100kg) followed by an ↑ to weekly based on clinical response and if weight is > 100kg then 162mg SC weekly . It should be noted that in contrary to synthetic DMARDs, Biological DMARDs should not be combined.

❖ **Non –Pharmacological therapy**

non –pharmacological therapy like physical and occupational therapy play an important role, and therefore should be assessed by expert of these therapies.

❖ **Surgery in RA**

When RA failed to respond to systemic therapy then surgery may be indicated .some of the common surgical intervention that is carried out are, synovectomy, joint replacement, osteotomy (excision of the metatarsal heads in-patient with subluxation of the MTP joints) and neurosurgical intervention in patients with Atlanto-axial subluxation.

➢ **Anti-TNF therapy and TB**

Patients should have baseline chest X-ray and assessment of risk of infection with mycobacterium tuberculosis prior to starting treatment with anti-TNF inhibitor.

Patient with active TB

- Should receive standard chemotherapy
- They must complete 2 months full treatment before started on anti –TNF alpha treatment

Patients with past TB,

- Patient who has received previous adequate therapy → can be started on anti-TNF alpha therapy but need to be monitored regularly.

Scanned with CamScanner

- TB not previously adequately treated, chemoprophylaxis should be given before commencing anti-TNF alpha treatment.

What is the optimal TB screening test in-patient with previous TB?

Interferon gamma release assay, because

- Previous TB or previous BCG vaccination does not alter the test.
- Positive testing indicates a need for anti-tuberculous treatment alongside golimumab, for example isoniazid.
- Mantoux testing is less indicative of prior infection because it is likely to evoke a positive reaction in patients with previous TB or who have received BCG vaccination.

Patients with a normal chest-radiograph who have not started immunosuppressive therapy,

→ a tuberculin test is helpful.

Patients with a normal chest radiograph + already on immunosuppressive treatment

- The result of the tuberculin test is dampened and it is therefore not useful.
- An individual risk assessment should be made, if the annual risk of TB is greater than that of drug-induced hepatitis then chemoprophylaxis should be given. If not, the patient should be monitored and investigated early if symptoms consistent with TB develop.
- Chemoprophylaxis is generally with isoniazid for 6 months.
- Patients who test positive with either of QUANtiFERON Gold test and Elispot tests should be treated with chemoprophylaxis either isoniazid for 6 months, or dual therapy Rifampicin + INH for 2 months) at the same time as being started on anti-TNF alpha treatment.
- TNF-inhibitors should be stopped 2-4 wks before any major operation.

➢ **Rheumatoid arthritis and pregnancy**

- patients with early or poorly controlled RA should be advised to delay the conception until their disease is well-controlled
- : many patients with rheumatoid arthritis go into remission during pregnancy
- RA patients should be referred to an obstetric anesthetists due to the risk of Atlanto-axial subluxation

Medications in pregnancy and breast-feeding

- Methotrexate (teratogenic) and NSAIDs (1st trimester, risk of abortion) so they are absolutely contraindicated.
- methotrexate is not safe in pregnancy and needs to be stopped at least 3 months prior to conception
- NSAIDs may be used until 32 weeks but after this time should be withdrawn due to the risk of early close of the ductus arteriosus therefore **Paracetamol** is the oral analgesic of choice during pregnancy
- Leflunomide is not safe in pregnancy and should be stopped 2- year before conception
- Prednisolone, Sulfasalazine and hydroxychloroquine are safe in pregnancy

Corticosteroids→ relatively safe in pregnancy when used in low dose < 20 mg daily.

- low-dose corticosteroids may be used in pregnancy to control symptoms

Scanned with CamScanner

- The routine use of oral calcium and Vit D is recommended.
- Stress doses of steroids should be used during Labour and delivery if the mother received steroids (even low dose) for more than 2-3 weeks during pregnancy, and the neonate should be monitored for evidence of adrenal insufficiency and infection. The main maternal risks are hypertension, glucose intolerance, and osteoporosis.

➢ **Sulfasalazine** can be safely used during all stages of pregnancy; it is compatible with breast-feeding.

➢ **Azathioprine** can be used in pregnancy if Sulfasalazine and hydroxychloroquine are not controlling. During pregnancy continue current dose of azathioprine and add folic acid .Breast feeding is not recommended with azathioprine. **While** Prednisolone and hydroxychloroquine may be taken whilst breast-feeding. **However,** Cyclophosphamide, methotrexate, and Leflunomide are contraindicated in breast- feeding mothers.

➢ **Biologic therapies**: evidence is limited but they may be relatively safe during pregnancy. The main theoretical risk is immunosuppression of the neonate, except for certolizumab, which cross the placenta in minimal amounts.

Mixed Connective Tissue Disease & Overlap Syndrome

MCTD

Some patients have features of more than one type of rheumatic diseases and these patients have overlapping features of SLE, systemic sclerosis, rheumatoid arthritis and inflammatory myositis. In these patient, renal or central nervous system involvement is uncommon. However, pulmonary hypertension and interstitial lung disease are more common. These patients have higher titre of **RNP antibodies** but specific antibodies of the disease are **absent.**

OVERLAP SYNDROME

Some patients have features of more than one connective tissue disease (e.g., rheumatoid arthritis and SLE, SLE and systemic sclerosis) in the absence of high-titer anti-RNP antibodies .It is called overlap syndrome. In contrast to MCTD, specific antibodies of each disease may be **positive**

Scanned with CamScanner

VIVA OF SLE

How will you investigate this patient?

- **ANA** →95-99% sensitive and has the highest negative predictive but not specific
- **Anti-dsDNA**→ highly specific (>99%) but less sensitive (60%) and its level correlate with disease activity
- **Anti-smith (Sm)** →Highly specific (>99%) but less sensitive (30%)
- **Anti-Ro(SS-A) & anti-La(SS-B)**→only in 30% of SLE patients and associated with development of neonatal lupus and anti-Ro may also cause congenital heart block
- **Low C3 & C4** →but congenital deficiency may also predispose to SLE so therefore these tests must be interpreted with caution (studies of the other family members may help differentiate inherited deficiency from complement consumption in active SLE)
- **ENA profile** → to rule out MCTD
- **Serum antiphospholipid antibodies (+APTT)**
- **Skin biopsy** → from normal (direct immunofluorescence and may show immune complex deposition) and affected skin(histopathology)
- **ESR** → raised during active disease
- **CRP** →typically normal unless underlying infection
- **CBC** →anemia and thrombocytopenia
- **Coombs test** → haemolytic anemia
- **Urine R/E** →RBC caste and proteinuria may indicate lupus nephritis
- **RFTs**→ Derange RFTs may indicate lupus nephritis
- **Renal biopsy** →to stage lupus nephritis
- **LFTS**→ autoimmune hepatitis

How will you diagnose SLE?

SLE diagnosis is based upon SLICC Criteria and or more recently European League against rheumatism / American college of rheumatology (EULAR/ACR) criteria.

➢ **SLICC Criteria**

- Patients is labelled as SLE ,if any 4 or more of 11 criteria are met
- (MD SOAP BRAIN)

1. Malar rash
2. Discoid rash
3. Photosensitivity
4. Oral ulcers
5. Arthritis
6. Serositis
7. **Kidney disease**

a. > 0.5 g/day proteinuria, or
b. > 3 + dipstick proteinuria, or
c. Cellular casts

Scanned with CamScanner

8. Neurologic disease

a. Seizures, or

b. Psychosis (without other cause)

9. Hematologic disorders

a. Hemolytic anemia, or

b. Leukopenia (< 4000 / mcL [4× 109 / L]) or Lymphopenia (< 1500 / mcL [1.5× 109 / L]), or

c. Thrombocytopenia (< 100000 / mcL [100 × 109 / L])

10. Immunologic abnormalities

a. Antibody to native DNA, or

b. Antibody to Sm, or

c. Antibodies to antiphospholipid antibodies based on (1) / IgG or IgM anticardiolipin antibodies, (2) lupus anticoagulant, or (3) false-positive serologic test for syphilis

11. Positive ANA

➢ **EULAR/ACR (new Criteria)**

- ANA ≥1:80
- ≥10 total points indicates SLE
- At least one clinical criterion is required .Only the highest point value criterion from each domain is counted

Clinical Domains points	Immunologic domains Points
Constitutional	
Fever→ 2	
Cutaneous	
No scarring alopecia→2	**Antiphospholipid antibody**
Oral ulcers →2	**Anticardiolipin IgG >40 GPL**
Subacute cutaneous	**or anti-ß2GP1 IgG >40 units or**
or discoid lupus→4	**lupus anticoagulant→ 2**
Acute cutaneous lupus→ 6	**Complement proteins domain**
Arthritis	**Low C3 or low C4 → 3**
Synovitis in at least two joints	**Low C3 and low C4→ 4**
or tenderness in at least two joints, and at least 30 min of morning stiffness→6	**Highly specific antibodies**
Neurologic	**Anti-dsDNA antibody → 6**
Delirium→2	**Anti-Smith antibody→ 6**
Psychosis→3	
Seizure→5	
Serositis	
Pleural or pericardial effusion→5	
Acute pericarditis→6	
Hematologic	
Leukopenia→3	
Thrombocytopenia	

Scanned with CamScanner

Autoimmune haemolysis →4 **Renal** **Proteinuria >0.5g/24 hr →4** **Class II or V lupus nephritis →8** **Class III or IV lupus nephritis→ 10**	

What is Jaccoud's Arthropathy

- Gross deformities of the hands without joint damage or erosions
- caused by recurrent episodes of synovitis that damage tendon sheaths and slings resulting in joint deformity
- causes
- SLE
- Rheumatic fever
- Parkinson's disease, and
- Hypocomplementaemic urticarial vasculitis.

What are the clinical features of SLE?

Systemic features

Fatigue, fever, weight loss, and Lymphadenopathy

Skin

- malar (butterfly) rash(20%) that spares nasolabial folds
- Discoid rash→ scaly, erythematous, well-demarcated rash in sun-exposed areas. Lesions may progress to become pigmented and hyperkeratotic before becoming atrophic
- photosensitivity
- Raynaud's phenomenon
- livedo reticularis
- non-scarring alopecia

Musculoskeletal

- Arthralgia typically affecting the small joints of the hands, wrists, and knees and is the most common symptoms.
- non-erosive arthritis
- Raynaud's Phenomenon

Cardiovascular

- Pericarditis

Scanned with CamScanner

- Myocarditis
- Libman-sacks endocarditis
- IHD

Respiratory

- pleurisy and pleural effusion →the most common lung manifestation of SLE
- fibrosing alveolitis
- chronic interstitial pneumonitis

Renal

- Proteinuria
- glomerulonephritis (diffuse proliferative glomerulonephritis(class-IV) is the most common type)

Neuropsychiatric

- anxiety and depression
- psychosis
- seizures
- transvers myelitis ,chorea and lymphocytic meningitis as part of the spectrum of lupus cerebritis

GIT

- Mouth ulcer
- Peritoneal serositis→ may abdominal pain and ascites
- Mesenteric vasculitis →abdominal pain, bowel infarction or perforation
- Hepatitis

Haematological

Neutropenia lymphopenia, thrombocytopenia and immune –mediated haemolytic anemia

- The triad of fever, arthralgia and rash in a woman of childbearing age should alert you for possible diagnosis of SLE

What are the indications of high-dose steroids (250-1g methylprednisolone) in SLE?

- SLE induced cerebritis
- Myocarditis
- Glomerulonephritis
- Alveolar haemorrhage
- Haemolytic anemia
- Severe thrombocytopenia

How will you treat this patient?

Treatment depends on the severity and manifestation of the disease.

- Avoid sun exposure and apply broad spectrum UVA/UVB sunscreen (at least 30SPF)
- Milder skin lesion respond well to topical steroid and oral hydroxychloroquine as 2nd line agent followed by topical tacrolimus
- Minor joint symptoms can be treated with NSAIDs and hydroxychloroquine

Scanned with CamScanner

- To prevent flare, immunosuppressive therapy (azathioprine, mycophenolate mofetil and cyclophosphamide) should be initiated with tapering dose of steroids.

Lupus nephritis treatment

Treatment includes induction and maintenance phase.

Induction of remission

For induction of remission, mycophenolate mofetil (1g-1.5g BD), or cyclophosphamide along with high dose steroids, is given .Belimumab can also be used in combination with mycophenolate and cyclophosphamide for lupus nephritis. If patient is not responding to above treatment, we opt for tacrolimus or cyclosporine and if still refractory the rituximab or Belimumab are recommended (esp. Biopsy proven stage iii, IV and V) .There are two regimes for cyclophosphamide for induction of remission.

1. Euro-Lupus Regimen

According to this regimen cyclophosphamide, 500mg intravenously every 2 weeks for total 6 doses.

2. National institute of Health sciences

This regimen recommends 500-1g cyclophosphamide 3-6 monthly until remission is achieved. While for maintenance, IV infusion every 3- month is recommended.

Maintenance of the remission

For maintenance of remission, azathioprine or cyclophosphamide is used along with tapering dose of steroid. In cases, where prolong or higher doses of cyclophosphamide are used in female, GnRH analogs can be given to protect premature ovarian failure or sperm and oocyte collection and storage should be considered before treatment. It is noteworthy, that rituximab is reserved for life – threatening manifestation that is refractory to conventional therapy.

What the poor prognostic factors of lupus nephritis?

- Nephrotic range proteinuria
- Poor response to treatment
- ↓ C3 and C4 level
- AP2A positive and
- Male gender

Scanned with CamScanner

What are the WHO stages of lupus nephritis?

Classification category	Features
Class 1: minimal mesangial	Normal/minimal proteinuria, normal creatinine Earliest and mildest form of glomerular involvement
Class II: mesangial proliferative	Microscopic haematuria +/- proteinuria Hypertension uncommon and nephrotic syndrome plus renal insufficiency rarely seen
Class III: focal lupus nephritis	Haematuria, proteinuria, hypertension, reduced eGFR +/- nephrotic syndrome
Class IV: diffuse lupus nephritis	Most common and severe form of lupus nephritis Clinical features as for class III but also significantly low C3 and high dsDNA, especially in active disease
Class V: Diffuse membranous nephropathy	Nephrotic syndrome, microscopic haematuria, hypertension, normal/high creatinine Can present without other clinical or serological manifestations of SLE but electron microscopy features will distinguish it from the idiopathic form
Class VI: advanced Sclerosing lupus	Slowly progressive renal failure with proteinuria and bland urine sediment. Does not respond to treatment

Stage I&II does not need treatment (However, HCQ should be introduced to ↓ progression) while except VI all other should be treated and respond to therapy.

SLE and Pregnancy

- Unlike many autoimmune diseases (SLE) often become worse during pregnancy and the puerperium .There is risks of maternal autoantibodies crossing placenta that may cause neonatal complications include congenital heart block and neonatal lupus erythematous.
- strongly associated with anti-Ro (SSA) antibodies

Treatment

- **Azathioprine**→ A large body of evidence supports its use during pregnancy. Although it is less effective in the management of SLE with renal disease versus other options, balance of benefit risk makes it the preferred intervention.
- **Ciclosporin** →appears to be associated with premature delivery and low birth weight .Although it does not seem to be associated with malformations; this drives its use as an alternative to azathioprine in patients who fail to gain control of their disease. However , cyclophosphamide, methotrexate and mycophenolate are all contraindicated for use in pregnancy

Drug-Induced Lupus Erythematosus

- Caucasians are affected by drug-induced lupus more commonly than Afro-Caribbean's, whereas the inverse is true of idiopathic SLE.
- Affect the 50-70-year age group most commonly.

Scanned with CamScanner

- has a male: female ratio of 1:1

Culprit Drugs

Procainamide
hydralazine ,
Quinidine
Carbamazepine

Phenytoin
Lamotrigine
Anti-TNF alpha agents

- Interferons
- Statins
- Minocycline and isoniazid

Risk factors

Exact cause is unknown but some of the risk factors are as below

- strongly positive ANA
- HLA-DR4 phenotype (hydralazine-induced disease)
- slow acetylator status
- Slow acetylators have increased risk of isoniazid-induced peripheral neuropathy, and hydralazine or procainamide-induced systemic lupus erythematosus (SLE).
- large total daily doses of precipitating drugs

Features

- symptoms may appear some 3 weeks to 2 years after the onset of drug
- In drug-induced lupus not all the typical features of SLE are seen, with renal and CNS involvement is uncommon.
- Lack of cutaneous involvement (However, drug induced lupus due to interferon and due to anti-TNF agents, may present with malar or discoid rash, and may be anti-dsDNA antibody positive) .
- joint pains, myalgia and malaise are more common pulmonary involvement (e.g. pleurisy) are common
- Raynaud's is seen in around 25%

Laboratory features

- ESR and C reactive protein (CRP) are both markedly elevated,
- ANA is strongly positive (in 100%,)
- Hypergammaglobulinaemia.

Scanned with CamScanner

- Positive for anti-ssDNA antibody and negative for anti-dsDNA antibody.
- antihistone antibodies are positive in 95% of drug-induced lupus (but also 50-80% of idiopathic SLE3)
- anti-Ro, anti-Smith positive in around 5%
- C3/C4 levels are usually normal.

Clinical features which distinguish drug-induced lupus from idiopathic SLE

- Males and females are equally affected in drug-induced lupus, whereas idiopathic SLE affects females nine(9:1) times more frequently
- the age of onset is typically older in drug-induced lupus, but this depends on the age at drug exposure
- Fever, arthralgia, serositis, and ANA occur at least as frequently in drug-induced lupus as idiopathic SLE.
- Haematological, renal, CNS involvement, and double-stranded DNA autoantibodies are rare.

Treatment

- Typically, no further treatment is required after withdrawal of the precipitating drug but sometime low dose steroid is required to aid resolution

SLE and Antiphospholipid Syndrome

Some of the patients suffering from SLE may be complicated by secondary antiphospholipid syndrome characterized by hypercoagulable state (arterial or venous thrombosis), recurrent fetal loss and thrombocytopenia. Antiphospholipid syndrome is diagnosed when at least one of the following laboratory criteria and one of the following clinical criteria are met.

Scanned with CamScanner

Clinical criteria

Vascular thrombosis

- One or more clinical episodes of arterial, venous or small vessels thrombosis in any organ or tissue
- Thrombosis must be confirmed by appropriate imaging studies or histopathology
- Thrombosis on histopathology specimen must be present without inflammation of vessel wall

Obstetric morbidity

- One or more unexplained fetal death of a morphologically normal foetus at or beyond 10th week of gestation
- One or more premature birth of a morphologically normal neonate before 34th week of gestation due to placental insufficiency and/or eclampsia or severe pre- eclampsia
- Three or more consecutive early miscarriages before 10th week of gestations; with maternal and paternal factors such as anatomical, hormonal and chromosomal abnormalities should be ruled out.

Laboratory criteria

Medium to high levels of APLs antibodies detected on two or more occasions, at least 12 weeks apart

- Lupus anticoagulant, detected according to the guidelines of the International Society on thrombosis and haemostasis
- Anti-cardiolipin antibodies (IgG and/or IgM) at medium-high levels (>40 units or above the 99th percentile)
- Anti-B2-glycoprotein I antibodies IgG and/or IgM at medium-high levels (>40 units or above the 99th percentile).

Scanned with CamScanner

Additional important points

There are three types of antiphospholipid antibodies are associated with this syndrome: (1) anti-cardiolipin antibodies, it can produce a biologic false-positive test for syphilis (a positive rapid plasma reagin but negative specific anti- treponemal assay and IgG anti-cardiolipin antibodies are believed to be more pathologic than IgM. (2) Antibodies to beta-2-glycoprotein, and (3) a "lupus anticoagulant that paradoxically prolongs APT but is associated with a thrombotic tendency rather than a bleeding risk. Presence of the lupus anticoagulant is a stronger risk factor for thrombosis or pregnancy loss than is the presence of antibodies to either beta-2-glycoprotein 1 or anti- cardiolipin. It is also also associated with ↓ platelets counts (22-42% of the patients).

Treatment of Antiphospholipid Syndrome

- For thrombosis, patients should be given warfarin (INR of 2-3). Direct-acting oral anticoagulants are less effective than warfarin. Patients who have recurrent thrombotic events while taking warfarin may require higher INR (>3.0), but at the cost of ↑ risk of bleeding.
  - Venous thrombosis → anticoagulation for 3-6 months and if recurrent lifelong anticoagulation
  - For arterial thrombosis →lifelong anticoagulation is recommended (INR-3)
- During pregnancy, the combination of low-molecular-weight heparin (prophylactic dose) and low-dose aspirin (81 mg) should be given to prevent pregnancy complications. Anticoagulation is continued through pregnancy and the early post- partum period. However, if SLE pregnant women with positive antiphospholipid antibodies (without thrombosis) should take aspirin only.
- In patients with catastrophic APS (widespread thrombosis, thrombotic microangipathy and MOF), intravenous immunoglobulin or plasmapheresis plus intra- venous heparin and high doses of corticosteroids are given. Resistant disease may require rituximab and or eculizimab). It has mortality of 50%

Discoid Lupus Erythematous (DLE)

It is a variant of SLE in which skin involvement is the main feature

- It very rarely progresses to SLE (in less than 5% of cases) .Usually there is negative ANA and anti – DNA. It is characterized by follicular keratin plugs and is thought to be autoimmune in aetiology .The lesion are discrete plagues often erythematous covered by scales. These lesions most typically occur on the face, scalp, in the pinnae, behind the ears and on the neck they can exist in areas not exposed to the sun .The lesion can progress with active indurated erythema at the periphery
- Central atrophic scaring characteristic
- Diagnosis is made by lesion biopsy
- Lesion heal with atrophy scarring (may cause scarring alopecia) and pigmentation

Management:

- Topical steroid cream followed by oral hydroxychloroquine as 2nd line agent
- Avoid sun exposure

Scanned with CamScanner

Spectrum of skin involvement without systemic disease

- Discoid lupus erythematosus (DLE)
- Subacute cutaneous lupus erythematosus (SCALE)
- Acute cutaneous lupus erythematosus (ACLE)

In SCALE there is ANA positive in 60 % patients however only 10-15% progress to SLE with moderate disease activity 80% of patients are anti-RO antibody positive.

What are the Recent Advances in SLE?

Belimumab (a monoclonal antibody that inhibits the activity of B-cell growth factors) is FDA approved therapy for SLE patients who have not responded to standard therapy.

Scanned with CamScanner

APPROACH TO BACK PAIN
(Due to Ankylosing Spondylitis)

P/C

Lower Back Pain → 2 months

ODPARA-V (HOPI)

My patient presented with lower back pain for the last 2 months that is gradual in onset, progressive in nature and involves the lower part of the back causing him unable to bend forward to pick something from the ground.

Pain is moderate to severe in intensity (scale from 0-10) persist throughout day and night, aching and dull in character , partially relived with painkiller and activity while it worsen with rest and sometime radiate to buttocks alternatively . Pain in the back is associated, with morning stiffness that last more than 30 minutes and improves with activity, and large joints pain like Knee pain, ankle joints and redness of the eyes. However, there is no HX of …

Now exclude relevant **DDs** of lower backache

- **Disc prolapsed or fracture of vertebra** → there is no Hx of trauma , lifting heavy objects that caused lower back pain radiating to lower limb
- **Potts Disease (TB)** → there is no HX of contact with TB patients, night sweat, fever and lower limb weakness.
- **Spinal abscess**→ there is no HX of painful swelling in the back associated with rigor, chills and back pain
- **Spinal metastases** →there is no HX of unintentional weight loss , ↓appetite and lumps &bumps in the body associated with back pain
- **Ankylosing Spondylitis(AS) → see care**
- **Spinal stenosis** →there is no HX of reliving back pain on bending forward and walking uphill
- **Multiple myeloma(Old age)**→ there is no HX of pallor of complexion , constipation , body aches associated with back ache
- **Osteomalacia** → there is no HX of inadequate sun exposure , ↓ milk intake and poor nutritional diet
- **Brucellosis** → there is no HX of contact with animal , ingestion of unpasteurised milk
- **HIV** → there is no HX of high risk sexual behaviour and IV abuser associated with back pain
- **Hyperparathyroidism** → there is no HX of excessive thirst , flanks pain and psychiatric problems
- **Hyperthyroidism**→ there is no HX of heat intolerance and palpitation
- **Fibromyalgia**→ there is no HX of painful points on the body associated with back pain
- **Paget disease** → there is no HX of raised ALP associated with back pain
- **RA** → Although it is commonly believe that RA does not present with back pain , however , RA is one of the differential diagnosis of morning pain with stiffness that improve with exercise **(Ref→Gautama Mehta)**

Scanned with CamScanner

- **Seronegative spondyloarthropathies(except AS)→** there is no HX of silver scaly skin lesion, bloody diarrhoea and joints pain associated with redness of eyes and painful micturition

CARE or RECA of AS

Remember 9S as Associations and Complications of AS

1. **Atlantoaxial subluxation** → HX of neck pain , numbness , tingling and weakness in the limbs
2. **Apical Fibrosis** → HX of dry cough or SOB
3. **Anterior uveitis**→ HX of redness of the eyes
4. **Aortic regurgitation** → HX of palpitation or SOB , and or chest pain (Angina)
5. **AV block** → HX of dizziness and or slow pulse (bradycardia)
6. **Amyloidosis**→ HX of large tongue and frothy urine (Nephrotic Syndrome)
7. **IgA nephropathy** → HX of blood in the urine
8. **Achilles tendonitis** →HX of pain on back of the heal
9. **PlantAr fasciitis** → HX of pain on the bottom of feet that is worse on walking after sleep or rest.
10. also ask

- Scaly silver skin lesion →psoriatic arthritis
- Bloody diarrhea and oral ulceration → (IBD)enteropathic arthritis
- Joint pain, painful red eyes and burning micturition → reactive arthritis.
-

Now ask **relevant**

ITP (investigation, treatment and procedures) **and**

PAM-HUGS-FOSS-TV -F

Examination

EXAMINATION OF BACK

Adequate exposure, politely ask (male) patient to remove the shirt

1. INSPECTION:

Look for gibbus formation, kyphosis, scoliosis, rash, or psoriasis.

In context of AS, look for **question mark sign** (occurs in advanced disease due to combination of thoracic hyperkyphosis, loss of lumbar lordosis, neck flexion deformities)

Gait should be assessed.

2. **PALPATION:** Examine for vertebral tenderness (with fist)

RANGE OF MOTION:

Cervical spine: Flexion and extension and lateral rotation

Thoracolumbar spine: Assess forward flexion, backward flexion and lateral flexion

SPECIFIC TESTS:

- **Wall to Occiput distance** : with patient's heels and buttocks touching the wall, measure distance between wall and occiput of patient (normal= 0 to 2 cm)
- **Wall to tragus distance** : (normal = below 10 cm)
- **Chest expansion** : reduced in AS

Scanned with CamScanner

- **Modified Schober's test**: Mark one point at the level midway between two PSIS and other 10 cms above it . Ask patient to bend forward without bending their knees, measure the distance by standing behind when patient is bent forward. If it's less than 15 cm, it is said to be positive.
- **Finger to floor distance**: Measure distance between middle finger of patient and floor with patient standing against the wall in neutral position .With patient maximally bent laterally, again measure distance between middle finger and floor (distance between both positions = > 10 cm)
    - Ask patient to lye on the examination couch and examination for any peripheral joint swelling (especially knees, ankles), tenderness at sites of Achilles tendon insertion and in heels for plantar fasciitis.
    - In relevant examination,

Ascultate apices of lungs for apical fibrosis and precordium for murmur of AR

Examine eyes for any redness secondary to uveitis and hands and feet for dactylitis.

Based on HX and examination, my clinical diagnosis is AS

- DDs depending on your actual case
- Enteropathic arthritis
- Psoriatic arthritis
- RA

Scanned with CamScanner

VIVA OF ANKYLOSING SPONDYLITIS

How will you investigate this patient?

- **Plain X-ray of sacroiliac Joint → may be normal early in the disease, the later changes include**
- straightening of lumbar spine caused by loss of lordosis
- "Squaring" of vertebrae due to erosion and sclerosis of the anterior corners of the vertebrae
- Bridging syndesmophytes due to calcification of the outermost fibres of the annulus.
- Ossification of the anterior longitudinal ligament (Dagger sign) and facet joint fusion.
- The combination of all these features results in the typical "bamboo" spine
- Atloaxial dislocation is a late feature
- **MRI→ more sensitive than x-ray and it may show**
- Obliteration of the sacroillac joint
- Bone marrow edema (the earliest feature)
- And other features as mentioned above
- **Spirometery→ restrictive pattern**
- **Dexa Scan** → as part of fragility fracture assessment
- **ESR & CRP** → may be raised in active disease but may be normal
- **CBC** → anemia (of chronic disease)
- **ECG & ECH** → heart block and MVR and AR
- **HRCT/X-Ra** → lung fibrosis
- **Urine R/E** → proteinuria due to amyloidosis

What is Modified [illegible] Test?

- Locate L5 Spinous Process
  - Level of Posterior Superior Iliac Spine
  - Dimples of Venus
- Mark points 5cm below and 10 cm above
- Have patient touch their toes
- Measure distance between marks
- Normal > 5 cm
- Abnormal < 2.5 cm

What is Wall /Flesche Test?

- Ask the patient to stand with his back to the wall
- Heels, buttocks, scapulae and occiput should touch the wall simultaneously
- AS patients are unable to do this test

What is Tragus to wall test?

Patient stand with heels and buttocks against the wall
The head is placed back as possible keeping the.chin
Horizontal
Normal: <15cm

Scanned with CamScanner

What are the modified New York criteria for diagnosis for AS?

It include clinical criteria and radiological criteria

Clinical Criteria:

- Low back pain, present for more than 3 months, improved by exercise, but not relieved by rest.
- Limitation of lumbar spine motion in both the sagittal and frontal planes.
- Limitation of chest expansion relative to normal values for age and sex.

Radiological Criteria:

- Sacroillitis on x ray
- Definite AS: If the radiological criterion is present plus at least one clinical criterion.
- Probable AS: If three clinical criteria are present alone or if the radiological criterion is present, but no clinical criteria are present.

Define ankylosing spondylitis

Ankylosing spondylitis is defined symptomatic sacroillitis (Persistent pain and stiffness for > 3 months) associated with morning stiffness and improvement on exercise or worsening with rest. The hallmark of the disease is sacroillitis. Patients with a history of back pain and morning stiffness, which is relieved by exercise or worse with rest, should undergo plain radiography of the sacroiliac joints. Plain radiography is usually sensitive enough to demonstrate sacroillitis, and severity is graded from 0 (normal) to IV (fused). If plain radiography is normal but suspicion remains high, MRI is warranted, since it is the most sensitive and specific investigation for sacroillitis.

What is the difference between mechanical and Inflammatory back pain

Features	Mechanical Back Pain	Inflammatory Back Pain
Age	Any	Below 40 Years
Onset	Acute	Insidious
Family History	Absent	Usually Present
Morning Stiffness	Absent	Present
Activity	Worse	Improve
Rest	Improve	Worse
Movement	Asymmetrical Restriction	Symmetrical Restriction

What are the systemic manifestations of ankylosing spondylitis?

- Anterior uveitis(up to 40% of patients)
- Aortic regurgitation, mitral valve prolapse and A-V conduction defects.

Scanned with CamScanner

- Apical pulmonary fibrosis and costovertebral rigidity
- Atlanto-axial subluxation →neurological sequelae may result from it or fractures of ankylosed spine, or cauda equina syndrome
- Achilles tendonitis→ enthesitis is a feature of the disease, particularly Achilles tendonitis and plantar fasciitis
- Amyloidosis
- IgA nephropathy

Are the peripheral joints involved in ankylosing spondylitis?

Peripheral joint involvement occurs in at some stage in 20-30% of patients, particularly in young patient. The knees and hips are most commonly affected

What do you understand by the term 'seronegative arthritis?

Seronegative arthritis refers to a group of overlapping conditions, such as psoriatic arthropathy, enteropathic arthritis, ankylosing spondylitis, and reactive arthritis (PEAR). The conditions are characterized by:

- Asymmetric oligoarthritis, particularly affecting the spine
- Association with HLA-B27 and anterior uveitis
- Absence of rheumatoid factor

What do you know about the genetics of ankylosing spondylitis?

- The HLA-B27 antigen is present in 95% of Caucasian patients with ankylosing spondylitis. By contrast, HLA-B27 is present in 8 %of healthy adults, and only 6% of patients. Testing for HLA-B27 is unnecessary, as the diagnosis is usually clinically and radiologically apparent.

What is the management strategy for ankylosing spondylitis?

General measures

- Patient education-genetic counselling i, since the risk of transmitting the HLA-B27 antigen to 50% offspring offspring
- Physiotherapy is the cornerstone of management, by preserving spinal mobility.
- Occupational therapy

Pharmacological treatment

- NSAIDS→ first line treatment and it may slow the radiographic progression of spinal disease.
- Local corticosteroid injection may be helpful for peripheral arthritis, planter fasciitis and other enthesopathies. Oral corticosteroids may be required for uveitis but do not have role in the spinal disease.
- DMARDs, Gold and penicillamine have no role in the treatment of ankylosing spondylitis. Methotrexate and sulphasalazine have some effect on peripheral disease, but not on the spine.

Scanned with CamScanner

- Biological therapy-anti-TNF-a therapy like adalimumab and etanercept , have established efficacy for NSAID-resistant axial disease and may slow the progression of AS
- IL-17 inhibitor like Secukinumab and ixekizumab are also effective modality of treatment for AS
- Arthroplasty → for severe hip , knee and shoulder arthritis with secondary osteoarthritis
- Spinal osteotomy →to correct posture.

Prognosis

The severity of the disease varies greatly and about 10% of the patients having work disability after 10 years. Hip involvement during the first 2-year is worse prognostic sign.

Brief discussion about other seronegative spondyloarthropathies

Psoriatic arthritis

Psoriasis precedes arthritis in 80% of cases. Arthritis usually asymmetric, with "sausage" appearance of fingers and toes (ductility's), but some time may present as polyarthritis (≥ 5 joints) that may resemble rheumatoid arthritis. Psoriatic arthritis commonly involve sacroiliac joint.

What are the types of psoriatic arthritis?

- Symmetrical psoriatic Poly arthritis
- Asymmetrical oligoarthritis
- Distal interphalangel predominant
- Spondylitis (sacroiliac joint involvement)
- Arthritis mutilans

What are the variant of psoriasis?

- Chronic plaque psoriasis (most common)
- Pustular psoriasis
- Guttate psoriasis
- Palmoplantar psoriasis
- Erythrodermic psoriasis(most severe form and life threating one)

What are the factors that may exacerbate the psoriasis?

- Trauma (new lesions often appear at sites of injury or trauma called koebner phenomenon)
- Alcohol
- Drugs
    - Beta blockers
    - ACEIs
    - Lithium
    - Anti-malarial like HCQ
    - NSAIDs

Scanned with CamScanner

- Penicillin & tetracycline
- Withdrawal of systemic steroid

- Search for psoriatic rash in scalp, behind the pinna, umbilicus and gluteal cleft (just mention this to examiner).

Enumerates possible nail changes in psoriatic arthritis

These changes are variable and with a wide range of results

- Nail pitting
- Onycholysis
- Horizontal ridging (Beau' s line)
- Dystrophic keratosis
- Yellowish discoloration of the nail plate
- Leukonychia
- Splinter haemorrhages and subungual haemorrhage

Investigation

Diagnosis is clinical

- **ESR & CRP** → is elevated in approximately 50% of patient's psoriatic arthritis.
- **Uric acid levels**→ may be high, reflecting the active turnover of skin affected by psoriasis
- **X-ray hands** →There are marginal erosions of bone and irregular destruction of joints and bone in the phalanx, may give the appearance of a **sharpened pencil.**
- **MRI sacroiliac joints** →a Psoriatic spondylitis causes asymmetric sacroillitis and syndesmophytes.

What is the CASPAR criterion for psoriatic arthritis?

Inflammatory articular disease (joint, spine or enthuses) with ≥3 points from the following (1 point each unless stated):

- Current psoriasis (scores 2 points)
- History of psoriasis in first- or second-degree relative
- Psoriatic nail dystrophy
- Negative IgM rheumatoid factor
- Current dactylitis
- History of dactylitis
- Juxta-articular new bone

Treatment

NSAIDs and analgesic may be sufficient for mild disease while intra-articular steroids can control isolated synovitis and enthesitis. Patients with spondylitis should be advised same exercise and

Scanned with CamScanner

postural regimen as discussed in AS. If patient is unresponsive to the conservative treatment, therapy with DMARDs should be considered like methotrexate and (being the drug of choice for arthritis and skin disease), other oral agents, such a Leflunomide, sulfasalazine, and cyclosporine may be effective. In patients with active psoriatic arthritis, a TNF inhibitor biologic agent is also recommended as first-line agent. If TNF inhibitor is contraindicated or not tolerated, who do not respond to TNF inhibitors or oral agents can be treated with ustekinumab(a monoclonal antibody that inhibits IL-12 and IL-23,) or secukinumab, guselkumab and ixekizumab, (inhibit IL-17. Tofacitinib (Jak-stat inhibitor) ,abatacept (CTLA4 inhibitor) and apremilast (PDE-4 inhibitor) may be options with failure of the above therapies. Systemic steroid are less effective in psoriatic arthritis than in other forms of inflammatory arthritis and may precipitate pustular psoriasis during tapers. Skin rash of psoriasis can be treated with topical steroid, Vit- D, tacrolimus, phototherapy (narrow band ultraviolet B light) and MTX.

Reactive arthritis

It is defined as an arthritis that develops following an infection where the organism cannot be recovered from the joint. It encompasses Reiter's syndrome (triad of urethritis, conjunctivitis and arthritis).

It is characterized by oligoarthritis, conjunctivitis, urethritis, keratoderma blennorrhagica, circinate balanitis, and sometime mouth ulcer. Very rarely, patient may develop carditis and aortic regurgitation .Usually there is HX of GI or genitourinary infection 1-4 backs and 50-80% patients are HLA-B27 positive.

Investigation

Diagnosis is clinical

- ESR & CRP→ may be raised
- Two glass test (to confirm urethritis) →the presence of mucoid threads in the first void specimen that clear in the second specimen confirm the urethritis
- High vaginal swabs → may reveal chlamydia on culture
- Stool culture → may be negative except for post-salmonella arthritis
- Joint aspiration(not commonly) → to exclude crystal induced arthritis or septic arthritis

Differential Diagnosis

Gonococcal arthritis can initially mimic reactive arthritis, but the marked improvement after 24-48 hours of antibiotic administration in Gonococcal arthritis and the culture results differentiate the two disorders.

Behcets disease may mimic reactive arthritis. The oral lesions of reactive arthritis, however, are typically painless, in contrast to those of Behcets disease.

Treatment

Scanned with CamScanner

NSAIDs have been the mainstay of therapy .There is no evidence for antibiotics unless a triggering infection is identified. For chronic reactive arthritis associated with chlamydial infection. 6 months of rifampin (300 mg order daily) in combination with either doxycycline 100 mg twice daily) or azithromycin (500 mg orally daily for 5 days then twice weekly) was more effective . Patients who do not respond to NSAIDs may respond to sulfasalazine or methotrexate. For those patients, that are refractory to NSAIDs and DMARDs, anti- TNF agents may be effective. Anterior uveitis is medical emergency, requiring topical, subconjunctival or systemic steroid

Enteropathic Spondyloarthritis

Patients ($1/5^{th}$) with inflammatory bowel disease may have arthritis, which complicates Crohn disease more than ulcerative colitis. In both diseases, two distinct forms of arthritis occur. The first is peripheral arthritis usually a nondeforming -asymmetric oligoarthritis of large joints (Knees, ankles, and hip) which the activity of the joint disease parallels that of the bowel disease. The arthritis usually begins months to years after the bowel disease, but occasionally the joint symptoms develop earlier and may be the presenting symptoms.

The second form of arthritis is a spondylitis (20-25%) that is indistinguishable by symptoms or radio- graphs from ankylosing spondylitis and follows a course independent of the bowel disease. About 50% of these patients are HLA-B27 positive.

NSAIDs can be effective when the arthritis is mild but must be used cautiously since they can exacerbate IBD. Instead judicious use of steroid, sulfasalazine and methotrexate may be an option .TNF inhibitors (except eternacerpt) is effective both for the bowel and for the joints. However, if MSK symptoms worsen despite TNF therapy, you should always exclude bacterial overgrowth as triggering cause (Blind-loop syndrome)

Scanned with CamScanner

APPROACH TO SKIN TIGHTNESS (Due to systemic sclerosis)

P/C worsening of skin tightness or
Difficulty in swallowing

HOPI (ODPARA-V)

My patient presented with worsening of skin tightness that is gradual in onset, progressive in nature and 6 months in duration .According to the patients, the tightness started in the hand & fingers and followed by involvement of forearm and face and as result patient was unable to make a fist, carry out fine movement like holding a spoon and open the mouth. However, according to the patient, he is able to carry out daily life activities like self-care. Additionally, my patient denied skin tightness in other part of the body like lower limb and abdomen. The Skin tightness is minimally relived with moisturizing ointment and liquid paraffin .The skin tightness is associated with bluish discoloration of the hands in cold, skin nodules on fingers, difficulty in swallowing solid food and reds spots on the body that blanches on pressure .However , there is no HX of

Now exclude DDs

- **Morphea(Localized scleroderma)** → there is no HX of localized skin tightness
- **Scleroderma**(without internal organs involvement) →there is no HX of sore throat followed by skin tightness in face and trunk
- **Eosinophilic fasciitis** →there is no HX of painful skin nodules over the tightness of skin area
- **Radiation /Chemo(bleomycin and vinyl chloride) induced skin tightness** →there is no HX of radiation or chemotherapy
- **Nephrogenic sclerosis**→ there is no HX of Gadolinium containing contrast MRI
- **Bone marrow transplant (GVH)**→No HX of bone marrow transplant
- **Amyloidosis**→ there is no HX of large tongue and chronic illness
- **Diabetic Cheiroarthropathy**→ there is no HX of excessive thirst , polyuria and raised blood sugar
- **MCTD**
- **Acromegaly** → headache , enlargement of hands and feet
- **Porphyria cutanea tarda** → HX of blister formation in sun exposed area

CARE/RECA (as systemic review)

- **CNS**→ trigeminal neuralgia→ HX of electric shock like sensation in the face
- **Resp** → ILD→ SOB on exertion and dry cough
- **CVS** →HTN and palpation, conduction defect and restrictive cardiomyopathy.
- **GIT** →GERD (due to smooth muscle atrophy and fibrosis in lower third of oesophagus), dysphagia and odynophagia, Ca oesophagus. Gastric outlet syndrome, watermelon stomach (due to antral vascular ectasia) and malabsorption diarrhea (due to bacterial overgrowth syndrome) and primary biliary cirrhosis (itching and yellow discoloration of sclera.

Scanned with CamScanner

- **Renal** →hypertensive renal crisis(it is much more common in diffuse cutaneous systemic sclerosis and patients with positive topoisomerase 1 and RNP antibodies) , haematuria and renal failure
- **MSK**→ arthralgia, flexor tenosynovitis , muscle weakness and wasting
- **Blood** → anemia (AIHA) and jaundice
- **Endocrinology** →hypothyroidism (cold intolerance)
- Other connective disorder **(MCTD)** →SLE(butterfly rash) RA (morning stiffness)
- **3 particular associations of systemic sclerosis are**

1. Adenocarcinoma lung
2. PBS
3. Hypothyroidism

Now ask about

RELEVANT

ITP (investigation, treatment and procedures) and

PAM-HUGS-FOSS-TV-F

Examination

If the command is GPE,

Start with vitals (BP should not be missed considering Lupus nephritis and Scleroderma renal crisis) followed by examination of hands (as mentioned in examination of hands)

Look for

- Assess skin thickness by pinching patient's skin between thumb and index finger,
- Assess extent of skin involvement { limited scleroderma if distal to elbows and knees , diffuse scleroderma if proximal to elbows and knees and truncal involvement} ,
- Look for ulcers, gangrene, auto amputated digits , Raynaud's phenomenon, sclerodactyly
- Hypertension and Pitting edema, signs of malignant hypertensive retinopathy on fundascopy { in case of renal crisis}
- Look for decreased oral aperture and peri-oral furrowing due to skin thickening along with prominent nose
- Telangiectasia's are usually present on hands, face ,tongue and chest
- Chest should be ascultated for features of ILD (end inspiratory bibasal crackles)
- Precordium should be ascultated for loud P2 secondary to Pulmonary arterial hypertension
- Abdominal examination to be done for any signs of pseudo-obstruction and small intestinal bacterial overgrowth (hypermobile gut)

{Aske the patient to put three fingers in mouth, commenting on nose as beaked nose or fish mouth should be avoided as this is considered disrespectful for the patients and is obsolete }

Systemic examination

Same as discussed in RA /SLE section

Scanned with CamScanner

VIVA OF SYSTEMIC SCLEROSIS

How will you investigate this patient?

- **CBC** →anemia
- **Peripheral smear** →microangioapthic hemolytic anemia in renal crisis
- **RFTs**→ abnormal in renal crisis and drug induced
- **LFTs**→ obstructive pic in case PBS and abnormal function due drug induced liver injury
- **ESR**→ usually normal and raised ESR is a bad prognostic sign
- **ANA** → positive in more than 95% and if it is negative consider an alternative diagnosis
- **Anti-SCL-70**→33% in diffuse SS while only in 20% limited variant of SS. It is also called anti-topoisomerase antibody and it impart poor prognosis, as it is strongly associated with interstitials lung disease.
- **Anti-centromere antibodies** →are positive in 50% of limited SS and 5% diffuse SS. It is highly specific for limited systemic sclerosis but may sometime also occours in overlap syndrome
- **Anti-RNA polymerase III**→ may be found in diffuse variant (10-20%) and associated with rapidly progressive skin disease , renal crisis and increased risk of cancer
- **Chest-X-ray and HRCT** → for ILD
- **X-ray hands** →tapering of terminal phalanges, resorption of distal phalanges and periarticular osteopenia
- **PFTs**→ restrtive lung disease
- **Echocardiography**→ cor-Pulmonale, to assess pulmonary HTN and pericardial effusion
- **ECG**→ conducting block
- **Barium swallow**→ to assess and grade esophageal involvement
- **Hydrogen breath test** → bacterial overgrowth
- **Skin biopsy** →thinning or absence of the epidermis

What are the American Rheumatism Association (ARA) diagnostic criteria for systemic sclerosis?

- Major features → skin sclerosis affecting arms , face and /or neck
- Minor features →sclerodactyly, finger pulp atrophy , bilateral pulmonary fibrosis
- 1 Major or ≥2 minor features are required to make a diagnosis

How many variants are there of systemic sclerosis?

1. **Limited (central) systemic sclerosis**

- The more common type of systemic sclerosis 70-80%
- Raynaud's may be first sign (seen in 90-95%)
- It mainly involves face , neck and distal limbs predominately
- associated with anti-centromere antibodies
- Previously known as CREST syndrome (Calcinosis, Raynaud's phenomenon, Esophageal dysmotility, Sclerodactyly, Telangiectasia).

Scanned with CamScanner

- **Pulmonary hypertension** is one the more common late complication and the most common cause of death.
- Malabsorption may also recognised complication
  - Can present with both diffuse and limited cutaneous forms.
  - Most GIT manifestations result from dysmotility secondary to infiltration of the intestinal wall with fibrous tissue.

II. Diffuse cutaneous systemic sclerosis (20- 30%)

- less common
- scleroderma affects trunk and proximal limbs predominately (although face may be involved in either type)
- associated with SCL-70 antibodies
- hypertension, **lung fibrosis** and renal involvement are commonly seen
- Pulmonary involvement is the second commonest organ involvement after Oesophageal disease and is the leading cause of death
  - **Pulmonary fibrosis** is associated with anti-Scl-70 antibodies in up to 70% of cases.
  - scl-70 antibodies associated with a higher risk of severe interstitial lung disease
  - Reduced DLCO is the earliest sign of pulmonary disease in systemic sclerosis, often before fibrotic changes manifest clinically.
- Diffuse cutaneous systemic sclerosis may lead to scleroderma renal crisis in up to 10% cases.

III. Scleroderma (without internal organ involvement)

Scleroderma is characterized by tightening and fibrosis of skin. It may be manifest as plaques (morphea) or linear.

IV. Scleroderma sine scleroderma

- Organ involvement without skin involvement

V. Malignant scleroderma

- An accelerated course of scleroderma leasing to death often in elderly men

How will you manage this patient?

Symptomatic and supportive care is the mainstay of treatment as no treatment can halt or reverse the fibrotic changes.

- Raynaud's phenomenon and digital ulcers

Avoidance of cold exposure, use of gloves/socks, avoids smoking; sue of lubricating lotion and maintenance of a high core temperature. If symptoms are persistent then, calcium channel blockers are the first line management. Slow release nifedipine (30-180 mg/day), amlodipine 5-20mg/day is effective therapy .Other options include losartan, fluoxetine, and sildenafil. Courses of intravenous prostacyclin (epoprostenol, ilopprost, and treprostinil) are used for severe disease and critical ischemia (e.g. 6-8 hours daily for 5 days). The bosentan (endothelin-1 antagonist) is indicated for treating ischemic digital ulcers.

➢ Hypertension and scleroderma renal crisis

- Aggressive treatment with ACE inhibitors is needed, even if renal impairment is present.

Scleroderma renal crisis (SRC)

Scanned with CamScanner

- The underlying mechanism is vasospasm
- Severe and life threatening renal disease develops in approximately 10-15% of patients. Characterize by severe hypertension, with diastolic BP over 100 mmHg, usually with grade III or IV hypertension retinopathy, together with rapid deterioration of renal function and heart failure symptoms of malignant hypertension, with headaches, blurred vision, fits, and heart failure.
- Haematological tests often demonstrate a thrombocytopenia and/or microangioapthic haemolysis.

Treatment of SRC

- Hypertension → ACE inhibitor (calcium channel blockers can be added).
- While ACE inhibitors are generally avoided in most patients with acute renal failure, scleroderma renal crisis is an exception to the rule as long as renal function is closely monitored.
- Renal dialysis may be required in severe case. An excessive reduction in BP or hypovolaemia should be avoided as ↓ renal perfusion → acute tubular necrosis. Thus, parenteral antihypertensive agents (such as intravenous nitroprusside or labetalol) should be avoided.

➢ Gastrointestinal complications

- Oesophageal reflux(GERD) should be treated by avoiding late night meal , small and frequent meals , remain upright for at least 2 hour after eating and with proton pump inhibitors and anti-reflux agents.
- Dysphagia is best managed with crushed and liquid meal along with oral prokinetic agents like metoclopramide(10mg times/day) , cisapride(10-20mg times/day) and if still resistant then erythromycin (250mg TDS)
- Malabsorption due to bacterial overgrowth may be treated with rifaximin (550 mg TDS)
- Pseudo obstruction may be treated with long term Octreotide(0.1mg SC daily) and prokinetic agents

➢ Joint and skin involvement

This may be treated with analgesics and NSAIDs. Methotrexate (7.5-20mg/ week) can be used in treatment of skin, arthritis, and myositis. Apart from myositis, steroid has no role in management of systemic sclerosis and higher dose may provoke sclerodermal renal crisis.

➢ Lungs Complications

- Interstitial lung disease

We have options like mycophenolate mofetil (1-1.5g BD) and if this is infective then cyclophosphamide is the mainstays of treatment in patients who have progressive interstitial lung disease. If both are ineffective or not indicated, then FDA Recently approved drug nintedanib (Multiple tyrosine kinase inhibitor) can slow progression of lung disease associated with systemic sclerosis.

Scanned with CamScanner

- Pulmonary hypertension

Pulmonary hypertension early treatment with bosentan is required. In severe or progressive disease, heart-lung transplant may be considered. Bosentan (, an endothelin receptor antagonist) improves exercise capacity in pulmonary hypertension and helps prevent digital ulceration. Phosphodiesterase type five inhibitors (sildenafil, tadalafil, vardenafil), a guanylate cyclase stimulant (riociguat), endothelin-1 receptor antagonists (bosentan, macitentan), and an endothelin-A receptor antagonist (ambrisentan) are used to treat pulmonary hypertension. Refractory pulmonary hypertension may require prostacyclin agonists (epoprostenol, treprostinil, iloprost) and patients with severe, diffuse systemic sclerosis; myeloablation followed by autologous stem cell transplantation is superior to cyclophosphamide but has greater toxicity.

- Cor –Pulmonale

As standard treatment of cor –Pulmonale like oxygen inhalation, diuretics and if resistant heart-lung transplant

➢ **Calcinosis and telangiectasia**

Laser therapy and sclerotherpay

What are the indications of systemic corticosteroid in SS?

- Inflammatory myositis
- Alveolitis
- Pericarditis

What are the poor prognostic factors?

- Old age
- Diffuse systemic sclerosis
- Low TLCO
- Pulmonary HTN
- Proteinuria
- Anti-SCL-70 antibodies
- Anti-RNA Polymerase III antibodies

What is the most important cause of mortality in SS?

- Renal failure

Prognosis

The 9-year survival rate in systemic sclerosis averages approximately 40%.

Mixed connective tissue disease

Mixed connective tissue disease (MCTD) is a condition in which some clinical features of systemic sclerosis, myositis, and SLE all occur in the same patient. It commonly presents with Raynaud's phenomenon and myalgias. Most patients have anti-RNP antibodies. Management focuses on treating the components of the disease.

Scanned with CamScanner

APPROACH TO MUSCLE WEAKNESS (Due to Dermatomyositis and polymyositis)

P/C Muscle Weakness .....4 months

Here we will briefly discuss the RECA and VIVA of Dermatomyositis (DM) and polymyositis (PM), for detail discussion on, how to approach the muscle weakness; reader is advised to see myasthenia gravis in neurology section.

RECA /CARE

- **Malignancy** (DM & PM) are notably associated with malignancy; therefore, you have to exclude malignancy in the body from head to toe
  - CA lung → HX of blood in sputum and hoarsens of voice
  - CA breast →HX of lump in the breast
  - CA stomach → HX of early satiety
  - CA ovary → HX of abnormal periods and heaviness in groin
  - CA colon → altered bowel habit and blood in the stool
- **ILD** → HX of SOB and dry cough
- **Rhabdomyolysis(AKI)**→ HX of ↓ urine output
- **MCTD**→ HX of oral ulcer , joints pain , photosensitivity and difficulty in opening mouth
- **Other autoimmune disorders** → HX of polyuria (diabetes) heat and cold intolerance (thyroid) and paleness of complexion (Pernious anemia).
- **Bulbar insuffiency**→ HX of difficulty in swallowing and invasive ventilation

Examination

GALE is the integral part of the examination.
If the command is GPE,

Start with vitals (BP should not be missed considering Lupus nephritis and Scleroderma renal crisis as spectrum of MCTD) followed by examination of hands (as mentioned in examination of hands) and look for

- Gottron's papules : erythematous macular rash over PIPs and/or MCPs
- Gottron's Sign : erythematous rash over elbows
- Heliotrope rash: violaceous rash over eyelids
- Malar rash : doesn't spare nasolabial folds in contrast to SLE
- Shawl sign : over upper back and shoulders
- V sign : hyperpigmentation over upper chest and neck
- Mechanic's hands : cracking fissuring rash on palms
- Raynauds phenomenon
- Power of Proximal muscles of both upper and lower limbs and neck flexors should be assessed

Scanned with CamScanner

- Chest should be ascultated for ILD
- Lymphadenopathy should be assessed as dermatomyositis is associated with high risk of malignancies

Systemic examination

Same as discussed in RA/SLE section

Scanned with CamScanner

VIVA OF DERMATOMYOSITIS (DM) & POLYMYOSITIS (PM)

How will you investigate this patient?

- **Creatine kinase and aldolase**→ 1st line investigation and it will be raised but normal level dose not exclude the diagnosis
- **ALT and AST** → raised and may be misdiagnosed as hepatitis
- **ESR and CRP** → normal and are not reliable indicator of disease activity
- **ANA (60%)and anti-Mi-2 (25%)**→ most common and specific antibodies for **DM** respectively
- **Anti-JO-1 antibodies(20-30%)** → more common in PM than DM
- **MRI** → demonstrate early and patchy muscle involvement and help localize site for biopsy
- **Muscle biopsy →definitive investigation and has distinct pattern for DM & PM**
  - **DM**→ perifascicular and perivascular cellular infiltrate
  - **PM**→ inflammatory infiltrate involve the fascicle itself

- **EMG** →Demonstrate that weakness is due to myopathic not neurogenic causes and abnormal in 90%
  - Short , small polyphasia motor units
  - Fibrillation and sharp waves
  - Bizarre , repetitive discharge
- **RA factor** →positive in minority of the patients
- **Screening for malignancy** → like Pan CT (whole body), mammography, transvaginal ultrasound (Ca ovary), CA -125 and PSA (prostate) etc.

How will you treat this patient?

Most patients respond to corticosteroids (1mg/kg) and are the mainstay if initial treatment. The dose is then tapper gradually (25%/month) while monitoring muscle strength and serum levels of muscle enzymes. However, Long-term use of corticosteroids (5-7.5mg) is often needed, and the disease may recur when they are withdrawn. Immunosuppressive drugs like methotrexate or azathioprine are often started as steroid sparing agents. Mycophenolate mofetil (1-1.5 g orally twice daily) and ciclosporin may also be useful as a steroid-sparing agent.

Intravenous immune globulin is effective for dermatomyositis resistant to prednisone. Rituximab is effective in some patients with inflammatory myositis unresponsive to prednisone.

The skin rash of dermatomyositis is often photosensitive; therefore, patients should limit sun exposure. Hydroxychloroquine can also help improve the skin disease.

Dermatomyositis due to underlying malignancy have a poor prognosis, although remission may follow treatment of the malignancy; corticosteroids may or may not be effective in these patients.

What are the characteristic features of DM?

- Shawl sign →macular rash over back and shoulder
- V-neck sign→ violaceous erythema involving the anterior chest

Scanned with CamScanner

- Holster sign →rash over the lateral aspect of thigh and hip
- Heliotrope rash in the periorbital region (pathognomonic sign)
- Gottron,s papules
- Finger telangiectasia →nail fold capillary dilatation

How will you differentiate B/w Steroid induced myopathy and myopathy due to active disease (DM &PM) itself?

Biopsy ll shows type II fibres atrophy in steroid induced myopathy while there is necrosis and regeneration in active myositis

What is dermatomyositis –sine myositis?

When there is only cutaneous manifestation without clinical evidence of muscle weakness. It is called dermatomyositis –sine myositis. Here serum muscle enzyme remain normal for few years

What are the types of DM/PM?

- Primary idiopathic dermatomyositis
- Primary idiopathic polymyositis
- DM /PM associated with underlying malignancy
- Juvenile dermatomyositis and polymyositis
- DM/PM associated with other connective tissue disorders

Scanned with CamScanner

How will you differentiate B/W DM, PM and inclusion body myositis?

	Polymyositis	Dermatomyositis	Inclusion Body Myositis
Onset	Subacute	Subacute	Slow
Age	Commonest < 50 years	Commonest < 50 years	Commonest < 50 years
Affected muscle	Proximal	Proximal	Proximal and distal
Symmetry	Symmetrical	Symmetrical	Asymmetrical
Common incidence	Female	Female	Male
Skin lesion	No	Characteristic rash	No
Creatine Kinase	Highly elevated (up to 50 fold)	Highly elevated (up to 50 fold)	Mild elevated(up to 10 fold)or may be normal
Antibodies	Anti-jo-1 are more common	Anti –mi-2-are highly specific	Anti-cN1A autoantibodies
Muscle biopsy	Endomysial mononuclear inflammatory infiltrate and muscle fibre necrosis.	perivascular and interfascicular inflammatory infiltrates with adjoining groups of muscle fibre degeneration/regeneration	
T cell	CD8 T cell	CD4 T CELL	Intranuclear or cytoplasmic tubofilaments
Response to steroid	Good	Good	Poor

Enlist certain situation when CPK may be normal in dermatomyositis

- Atrophy of the muscle due to long standing disease
- dermatomyositis –sine myositis as no muscle are involved
- DM associated with underlying malignancy

What are the other causes of raised CPK beside dermatomyositis and polymyositis?

- Muscle trauma (rhabdomyolysis)
- Convulsion
- Vigorous exercised
- Drugs like statin , busulphan , Chloroquine and colchicine
- Myopathies and myositis due to other cause

Proximal weakness with normal reflexes, sensation, and absence of fasciculation:

- Without skin lesion →polymyositis
- With skin lesion →dermatomyositis

Scanned with CamScanner

Myositis-specific antibodies

Antibody	Clinical Association
Anti-Jo-1 and other anti- tRNA synthetase antibodies	Polymyositis or dermatomyositis with interstitial lung disease, arthritis, mechanic's hands
Anti-Mi-2	Dermatomyositis with rash more than myositis, good prognosis
Anti-MDA5 (anti-CADM 140)	Dermatomyositis with rapidly progressive lung disease, cutaneous ulcers
Anti-TIF-1 (p155/140)	Cancer-associated dermatomyositis
Anti-NXP-2	Juvenile dermatomyositis
Anti-SAE	Cancer-associated dermatomyositis, dermatomyositis with pulmonary arterial hypertension
Anti-signal recognition particle	Severe, acute necrotizing myopathy
Anti-HMG CoA reductase	Necrotizing myopathy related to statin use
PM-Scl, Ku, U 1-3 RNP	Polymyositis/dermatomyositis over-lap syndromes

What is anti-synthetase syndrome?

This syndrome is characterized by myositis (PM), Raynaud, fibrosing alveolitis and mechanic's hand (thickened, cracking and peeling skin).

Cryoglobulinaemia

Cryoglobulinaemia are abnormal immunoglobulin which precipitate when cooled below 37° C and dissolve in plasma when warmed back to 37° C. in simple words its reversible precipitation at low temperature and can block blood vessel and cause toes and fingers to become ischemic (gangrenous). Cryoglobulins usually consist of IgM that is directed against the Fc region of IgG. These immune depositions on the small vessel wall result in vasculitis that presents with a reticulated skin due to micro-thrombosis and gangrene. Additionally, these immune complexes also activate the complement system resulting in ↓ complement level (↓C4).

Meltzer's Triad (typeII/III) → palpable purpura, arthralgia and myalgia.

Vasculitis rash and neuropathy (sensorimotor and or sensory) in a patient with HCV infection is highly suggestive of Cryoglobulenemia

Common causes of Cryoglobulinaemia

- Hepatitis C
- Multiple Myeloma
- SLE
- RA

Scanned with CamScanner

- Idiopathic

Types of Cryoglobulinaemia

Type I (25%)

- Monoclonal and consist of IgG or IgM
- Raynaud is the feature of type 1 only
- Commonly associated with myeloma and Waldenstrom macroglobulenaemia

Type II (25%)

- Mixed monoclonal and polyclonal
- It consist of monoclonal IgM RA factor and polyclonal IgG
- Commonly associated with HCV , RA , lymphoma and Sjogren syndrome
- Membranoproliferative GN on biopsy in case of renal involvement

Type III (50%)

- Polyclonal usually with RF
- Composed of a polyclonal IgM rheumatoid factor and polyclonal IgG
- Associated with RA and sjogren syndrome

- Type II & Type III is called mixed Cryoglobulenemia and is the most common type (80%) and strongly associated with HCV

Treatment

Treat the underlying cause along with immunosuppressive therapy. Plasmapheresis is indicated when it is refractory to the standard treatment.

Scanned with CamScanner

VASCULITIS

(Written by Dr.Quratulain Abbasi, FCPS Medicine, Resident Rheumatology)

Examination scheme

Vitals and In case of suspected vasculitis, after doing GPE (in both long and short case) ,

- Examine all possible pulses(bilaterally)
- Start with palpating Radial pulses bilaterally (compare volume and if one feeble or completely non-palpable) , followed by Brachial pulses , take BP on both arms , move on carotid and subclavian pulses , palpate temporal arteries bilaterally (at temples, carefully palpate for diminished pulsation on one side & cord like sensation (in Giant cell arteritis)
- Palpate for bilateral femoral arteries followed by popliteal and posterior tibial & dorsalis pedis arteries to complete lower limbs arterial examination.
- Ascultate for bruits over carotid and temporal arteries and for abdominal aortic aneurysm
- Ascultate precordium for murmurs
- Examine for stiffness and weakness of hip and shoulder girdles (Polymyalgia rheumatica)
- Examine for neuropathies (foot drop, wrist drop; common in Polyarteritis nodosa & Eosinophilic granulomatosis with polyangiitis)

Giant Cell Arteritis

History & Examination:

Fever, arthralgias, and headache

ODPARA-V of all the symptoms in detail

HOPE: Fever is insidious in onset, weeks to months in duration, low grade intermittent, persistent over the disease course, no diurnal variation, relieved by antipyretics but recurs. Associated with malaise and arthralgias, but no swelling of joints. Headache is insidious in onset, unilateral (mention right/left sided) temporal in location, moderate in intensity, associated with scalp tenderness (experienced during combing hair) & jaw claudication (experiences fatigue on chewing).

On examination, feel for temporal artery tenderness, patency bilaterally (involved site is feeble/not palpable).

Carotid and temporal Bruits should be ascultated.Examine for proximal myopathy (Polymyalgia rheumatica).

VIVA QUESTIONS:

1. How would you proceed with the workup in this patient

Answer:

- CBC showing anemia (normocytic normochromic) , thrombocytosis and leukocytosis
- Eelevation of the inflammatory markers ESR and CRP (high sensitivity, low specificity)
- Elevation of liver alkaline phosphatase
- temporal artery biopsy or other arterial biopsy (eg, occipital artery or aorta)
- Vascular imaging plays an increasingly important role in the diagnosis of GCA including **Color duplex ultrasound , MRI ,MRA & PET scan**

Scanned with CamScanner

2. What is most common vasculitis in adults:

Answer:

Gaint cell arteritis .GCA is the most common form of vasculitis in adults.

Llifetime risk after the age of 50 of 1% and 0.5% in women and men

3. What are symptoms you would ask considering suspicion of GCA:

Answer:

- Jaw claudication,
- Scalp tenderness (experienced by patient on combing hair),
- Hip and shoulder girdle stiffness and claudication's (as Polymyalgia Rheumatica i.e. PMR can occur in subgroup of GCA patients.
- Visual symptoms including Transient visual loss should be asked about.

4. What is gold standard investigation in GCA:

Answer:

Gold standard if suspecting GCA: A characteristic pattern of inflammation in a temporal artery or other arterial biopsy (eg. occipital artery or aorta) is the most specific test for the diagnosis of GCA. . granulomatous infiltrates composed of lymphocytes, macrophages, and giant cells. Disruption of the elastic lamina is frequently seen Length of at least 1–2 cm of vessel biopsy specimen is generally recommended.

Diagnostic Criteria

Diagnostic criteria	
If a patient possesses ≥3 criteria, GCA is diagnosed:	1. Patient age >50 years
	2. New-onset headache
	3. Temporal artery abnormality (tenderness to palpation or decreased pulsation, unrelated to atherosclerosis of cervical arteries)
	4. Elevated ESR ≥50 mm/h
	5. Abnormal TAB

Question: What is the most feared complication of GCA?

Answer:

The most feared complication of GCA is blindness, which can be prevented in the majority of cases by early diagnosis and prompt treatment with glucocorticoidcoids.

Blindness may occur in up to 20% of GCA patients, typically before the diagnosis is made and treatment with glucocorticoids is initiated.

Unfortunately, permanent vision loss is usually severe and irreversible

In more than 95% of cases, the mechanism of permanent vision loss is the occlusion of the posterior ciliary arteries that perfuse the head of the optic nerve causing anterior ischemic optic neuropathy (AION)

Scanned with CamScanner

Other complications may include aortic aneurysm, limb ischemia form arterial stenosis.

5. What can be the possible differentials of GCA

Answer:

ANCA-associated vasculitis, cryoglobulinemic vasculitis, and poly-arteritis nodosa, for can cause inflammation of the extra cranial arteries and produce headaches, scalp tender-ness, and jaw claudication.

6. Treatment options:

- There is no curative treatment for GCA.
- Pprolonged glucocorticoid tapering courses (eg, 12–18 months)

Prednisone (40–60 mg/day) should be administered immediately to any patient in whom GCA is strongly suspected while appropriate confirmatory workup is being completed to prevent visual loss.

- IL-6 inhibitor (Tocilizumab) therapy leads to a higher rate of sustained remission, less cumulative glucocorticoid exposure (brand : Actemra 162mg S/C weekly)

Randomized controlled trails ongoing with

- IL-6 inhibitor sarilumab ,
- JAK/STAT inhibitor updacitinib &
- GM-CSF receptor antagonist mavrilimumab

B.Takayasu Arteritis (Ta)

Presenting symptoms:

Constitutional symptoms, vessel pain/tenderness, or ischemia of extremities, uncontrolled hypertension

On **examination**

Pulses and BP in all four limbs

Check for bruits (carotid, subclavian), examine for abdominal aortic bruits, detailed cardiovascular examination for valvular pathologies

Takayasu arteritis is large vessel vasculitis; its natural history is as follows:

- **Phase I:** pre-pulseless, period characterized by systemic complaints, such as fever, arthralgias, and weight loss, often misdiagnosed as an infectious syndrome.
- **Phase II:** vessel inflammation, dominated by vessel pain and tenderness.
- **Phase III:** fibrotic stage, when bruits and ischemia predominate

Clinical manifestations:

i. Involvement of the subclavian (more commonly) and iliac arteries may lead to limb claudication.
ii. Carotid and vertebral artery involvement may lead to presyncope or headache.
iii. Pulmonary artery disease can occur with symptoms of pulmonary hypertension.
iv. Cardiac involvement with angina, myocardial infarction, heart failure, sudden death, and aortic valvular
v. Regurgitation occurs.
vi. Hypertension , arthralgias, and constitutional symptoms are common

Question: How will you proceed with workup?

Answer:

CBC: anemia of chronic disease, thrombocytosis, and an elevated ESR and CRP

Scanned with CamScanner

Imaging is required to make a diagnosis of TA.

MRA is the preferred initial modality for the diagnosis **Angiography** was the traditional gold standard for detecting arterial involvement in TA;

Hhowever, newer modalities are non-invasive and provide greater information about active inflammation.

Biopsy is not necessary to establish a diagnosis of TA.

Diagnostic Criteria:

2022 AMERICAN COLLEGE OF RHEUMATOLOGY / EULAR

CLASSIFICATION CRITERIA FOR **TAKAYASU ARTERITIS**

CONSIDERATIONS WHEN APPLYING THESE CRITERIA

- **These classification criteria should be applied to classify the patient as having Takayasu arteritis when a diagnosis of medium-vessel or large-vessel vasculitis has been made**
- **Alternate diagnoses mimicking vasculitis should be excluded prior to applying the criteria**

ABSOLUTE REQUIREMENTS

Age ≤ 60 years at time of diagnosis	
Evidence of vasculitis on imaging[1]	

ADDITIONAL CLINICAL CRITERIA

Female sex	+1
Angina or ischemic cardiac pain	+2
Arm or leg claudication	+2
Vascular bruit[2]	+2
Reduced pulse in upper extremity[3]	+2
Carotid artery abnormality[4]	+2
Systolic blood pressure difference in arms ≥ 20 mm Hg	+1

ADDITIONAL IMAGING CRITERIA

Number of affected arterial territories (select one)[5]	
One arterial territory	+1
Two arterial territories	+2
Three or more arterial territories	+3
Symmetric involvement of paired arteries[6]	+1
Abdominal aorta involvement with renal or mesenteric involvement[7]	+3

Sum the scores for 10 items, if present. A score of ≥ 5 points is needed for the classification of TAKAYASU ARTERITIS.

1. Evidence of vasculitis in the aorta or branch arteries must be confirmed by vascular imaging (e.g., computed tomographic/catheter-based/magnetic resonance angiography, ultrasound, positron emission tomography).
2. Bruit detected by auscultation of a large artery, including the aorta, carotid, subclavian, axillary, brachial, renal, or iliofemoral arteries.
3. Reduction or absence of pulse by physical examination of the axillary, brachial, or radial arteries.
4. Reduction or absence of pulse of the carotid artery or tenderness of the carotid artery.
5. Number of arterial territories with luminal damage (e.g., stenosis, occlusion, or aneurysm) detected by angiography or ultrasonography from the following nine territories: thoracic aorta, abdominal aorta, mesenteric, left or right carotid, left or right subclavian, left or right renal arteries.
6. Bilateral luminal damage (stenosis, occlusion, or aneurysm) detected by angiography or ultrasonography in any of the following paired vascular territories: carotid, subclavian, or renal arteries.
7. Luminal damage (stenosis, occlusion, aneurysm) detected by angiography or ultrasonography involving the abdominal aorta and either the renal or mesenteric arteries.

Scanned with CamScanner

Question: What is the treatment for TA?

Answer:

- High-dose glucocorticoids (prednisone, 30 mg twice daily) are the initial therapy for active inflammatory TA, followed by long-term taper after symptoms and laboratory evidence of inflammation normalize. Relapses are common, and about 20% of patients never achieve remission.
- About 50% of TA patients may require additional immunosuppressive therapy
- The best evidence base and clinical experience exists for methotrexate. Leflunomide, mycophenolate mofetil, azathioprine, ustekinumab, and infliximab have also been used in refractory cases.
- Cyclophosphamide is reserved as a salvage therapy.
- Besides immunosuppression, BP control, antiplatelet therapy, tobacco cessation and lipid management are essential to reduce cardiovascular risk.
- Angioplasty, stenting, and bypass graft surgery are indicated for symptomatic stenotic lesions that do not improve with medical therapy.

C.Polyarteritis Nodosa (PAN)

It should be considered in any patient who has new onset hypertension, skin manifestations (reticular net like pattern on lower limbs), abdominal pain and neuropathy (mononeuritis multiplex)

Question: What is [illegible]?

Answer:

PAN is a multisystem condition ccharacterized by inflammation of small and medium-sized arteries. Patients present with symptoms related to peripheral nerves, skin, abdomen, muscle, and kidney in decreasing order.

Involvement of lungs and ears/nose/throat is unlikely and should make one think of another diagnosis.

Question: Name medium vessel vasculitides

Answer:

- Polyarteritis nodosa (PAN).
- Kawasaki's disease
- Thromboangiitis obliterans (Buerger's disease).

Question: What are the clinical features suggestive of PAN?

Answer:

- Sskin lesions (palpable purpura, livedo, necrotic lesions, infarct of the fingertips),
- Pperipheral neuropathy (most frequently mononeuritis multiplex),
- Abdominal pain (mesenteric vasculitis), and hypertension with microscopic hematuria/proteinuria.

Question: What are the conditions associated with PAN include:

Scanned with CamScanner

Answer:

- **Viral infections**

(HBV >cytomegalovirus, human T-lymphotropic virus1, HIV, parvovirus, Epstein–Barr virus, hepatitis C [rare]).

- Autoimmune disorders (SLE,RA,childhood dermatomyositis)
- Hairy cell leukemia

Question: What labs parameters are positive in PAN?

Answer:

- Elevated (ESR)/ (CRP), anemia, thrombocytosis, and diminished levels of albumin are usually present.
- Hepatitis B surface antigen (HBsAg) is present in 10% to 50%. Patients with hepatitis B-associated PAN will also be hepatitis B envelope antigen (HBeAg) and HBV DNA-positive.
- ANCAs, RF, ANA, & cryoglobulins should be negative in classic primary PAN.
- Decreased complement levels are unusual.
- Once you suspect PAN, **biopsy** of accessible tissues should determine the diagnosis

The pathologic lesion defining classic PAN is a **focal and segmental Transmural necrotizing vasculitis** of medium sized and small arteries.

Renal biopsy should be avoided due to risk of aneurysmal rupture.

The angiographic findings in PAN:

Small saccular aneurysms (micro aneurysms), luminal irregularities, and stenosis of the small and medium-sized vessels of the viscera.

A characteristic string of aneurysms in an artery is called the "rosary bead sign". Angiography has sensitivity of 90%.

Diagnostic Criteria for Pan:

3 Or More of Following Features Establishes Diagnosis Of PAN

Scanned with CamScanner

TABLE 1: American College of Rheumatology 1990 polyarteritis nodosa diagnostic criteria.	
1	**Weight loss of more than 4 kg which is not related with diet or other factors from the beginning of the disease**
2	Livedo reticularis
3	**Testicle pain or tenderness**
4	Muscle pain, pain and weakness in the muscles of the legs
5	**Mono- or polyneuropathy**
6	Diastolic blood pressure > 90 mmHg
7	**Increase in blood urea or creatinine level which is not related with dehydratation or obstruction**
8	Presence of Hepatitis B surface antigen or antibody
9	**Abnormal celiac or renal angiography**
10	Findings including polymorphonuclear leukocytes in the medium-small arteries on tissue biopsy.

Question: How do you treat PAN?

Answer

For mild disease

(Constitutional symptoms, arthritis, anemia, skin lesions, normal glomerular filtration rate without cardiac, gastrointestinal, or neurologic involvement)

Iinitial treatment with prednisone 1 mg/kg per day for 4 weeks and then slow taper over 6 to 12 months if in remission.

Aazathioprine (2 mg/kg) or methotrexate (20–25 mg weekly) can be added.

For **moderate to severe disease:**

Ttreatment should include high doses of glucocorticoids and cyclophosphamide

Rx for HBV related PAN:

Ppatients who are HBsAg and HBeAg-positive are treated with a combination of Prednisone Img/kg/day for 1 week to control systemic symptoms, and off by the end of the 2nd week.Plasma exchange to remove circulating immune complexes (3 times/week for 3 weeks, 2 times/week for 2 weeks, then 1 time/week until HBeAg-negative).Anti-hepatitis B viral agents to eliminate the virus. Give antiviral agent on days of plasma exchange after the procedure to maintain an adequate blood level.

D. ANCA Associated Vasculitides

Scanned with CamScanner

Question: What are ANCA associated vasculitides?

Answer:

- Granulomatosis with polyngitis (formerly known as Wegener's granulomatosis
- Microscopic polyngitis (MPA)
- Eosinophilic granulomatosis with polyangiitis (EGPA)

D1. Granulomatosis with Polyangiitis

- History of recurrent upper respiratory (sinusitis, pharyngitis, laryngitis) and lower respiratory tract infections.
- History of ATT (anti tuberculous treatment) is positive due to cavitating granulomas on Chest X-rays.
- All organ systems may be affected to variable degrees by GPA.
- Constitutional symptoms such as anorexia, weight loss, fatigue, malaise, and fever are common.

Systemic symptoms that should be inquired and looked for on examination include:

Eye: commonly involved, affecting 30% to 60% of patients. Proptosis due to orbital inflammatory disease affects may result in loss of visual acuity as a result of impingement upon the optic nerve.

Ear: inner ear involvement can produce vertigo or hearing loss (Conductive hearing loss and mixed hearing loss (conductive and sensorineural). Otitis media in an adult is a strong clue to the diagnosis of GPA.

Skin: Lesions include palpable purpura, ulcers, subcutaneous nodules, vesicles, and livedo reticularis

Neuropathy: The most common peripheral neuropathy is mononeuritis multiplex .

Inquire about frothy urine as FSGS occurs in 30% of patients

On **examination**, look for saddle nose deformity (destruction of nasal septum due to chronic recurrent sinusitis) and chest examination may reveal reduced air entry and increased vocal resonance (cavitation)

Question: Which ANCA antibodies are positive in GPA?

Answer: Among GPA patients with positive ANCA, 80% to 90% are c-ANCA-positive with PR3 specificity, whereas 10% to 20% are p-ANCA-positive with MPO specificity.

The overall specificity of PR3-ANCA for active generalized GPA is 98%.

Question: What are other lab parameters positive in GPA?

Answer:

- Anemia of chronic inflammation, leukocytosis, thrombocytosis, and elevation of ESR & CRP.
- Low serum albumin and elevated globulin levels.
- Evidence of glomerulonephritis is suggested by the presence of hematuria, pyuria, cellular casts, and proteinuria with or without elevated serum creatinine.
- CXR and Ct chest with contrast, CT PNS.

Scanned with CamScanner

- electrocardiography and echocardiography for pericarditis, nerve conduction velocity for mononeuritis multiplex, and MRI for suspected Oorbital inflammatory disease.
- Non-caseating granulomas in biopsy of involved tissue/organ are confirmatory.

Question: What are the prototypic pulmonary-renal syndromes?

Answer: The prototypic pulmonary-renal syndromes are

- Granulomatosis with Polyangiitis
- Mmicroscopic Polyangiitis
- Goodpasture disease, and
- SLE

Diagnostic Criteria for GPA

Items	Score
Score for the ACR/EULAR 2017 provisional classification criteria for GPA	Sum≥5
Bloody nasal discharge, ulcers, crusting or sinonasal congestion	3
Nasal polyps	-4
Hearing loss or reduction	1
Cartilaginous involvement	2
Red or painful eyes	1
C-ANCA or PR3-ANCA	5
Eosinophil count ≥1 (×10⁹/L)	-3
Nodule, mass or cavitation on chest imaging	2
Granuloma on biopsy	3

ACR, American College of Rheumatology; EULAR, European League Against Rheumatism; GPA, granulomatosis with polyangiitis; C-ANCA, cytoplasmic antineutrophil cytoplasmic antibody; PR3-ANCA, proteinase 3-ANCA.

Question: How will you manage GPA?

Answer:

- Nasal irrigations to prevent sinus infections and cyclic antibiotics for recurrent LRTIs.
- High-dose oral or intravenous (IV) pulse corticosteroids are given as initial therapy, with gradual dose reduction.
- Cyclophosphamide (NIH Lupus nephritis protocol) can be used.
- RITUXIMAB is now considered more effacious and safe option in comparison with Cyclophosphamide
- To maintain remission, Azathioprine and Methotrexate can be used.

D2. Question: What is microscopic polyangiitis (MPA)?

Answer: MPA is defined as a systemic necrotizing vasculitis that clinically and histologically affects small vessels (i.e. Capillaries, venules, or arterioles) with few or no immune deposits. Frequently it is associated with focal segmental necrotizing GN and pulmonary capillaritis. It can be separated from classic PAN primarily because it does not cause microaneurysm formation of abdominal or renal vessels. It can be differentiated from GPA in that it does not cause granuloma formation or a granulomatous vasculitis. P-ANCA directed against MPO is found in up to 60% of patients. 15%–30% may have c-ANCA.Treated on lines of GPA.

Scanned with CamScanner

D3. EGPA (eosinophilic granulomatosis with polyangiitis)

EGPA, also known as Churg–Strauss Syndrome, is a granulomatous inflammation of

Small- and medium-sized vessels, frequently involving the skin, peripheral nerves, and lungs, which is associated with peripheral eosinophilia.

IMPORTANT POINTS IN HISTORY:

- It occurs primarily in patients with a previous history of allergic manifestations, Such as rhinitis (often with nasal polyps; 70%) and adult-onset asthma (>95%).
- Mononeuritis multiplex or asymmetric sensorimotor polyneuropathy; rarely central nervous system or cranial nerve involvement
- Subcutaneous nodules, Petechiae, purpura, skin infarction, (they occur mainly during the vasculitic phase)

Question: What are the laboratory abnormalities in EGPA?

Answer:

- The characteristic laboratory abnormality is **eosinophilia** (>1500 cells/μL).
- Anemia, elevated ESR/CRP, elevated IgE, and a positive rheumatoid factor may be found.
- ANCAs are present in 50% to 65% of patients. These are directed primarily against MPO and give a P-ANCA pattern.

Question: How do you diagnose EGPA?

Answer:

The diagnosis should be suspected in a patient with a previous history of allergy or asthma who presents with eosinophilia (>1500/μL), and systemic vasculitis involving two or more organs. The diagnosis is econfirmed by biopsy of the involved tissue, showing **small necrotizing granulomas,** as well as **necrotizing vasculitis of small arteries and veins.**

Question: How do you treat EGPA?

Answer:

- The treatment of choice is Gglucocorticoids.
- Those with severe presentations may benefit from 3 days of pulsed methylprednisolone (1 g/day).
- Up to 10% of patients are resistant to conventional therapy. These patients may benefit from mepolizumab or rituximab.
- Mepolizumab,an antibody to IL-5, was approved by the FDA for treatment of EGPA late in 2017 and is the first medication to receive FDA approval for EGPA

Scanned with CamScanner

DIAGNOSTIC CRITERIA FOR EGPA

2022 AMERICAN COLLEGE OF RHEUMATOLOGY / EUROPEAN ALLIANCE OF ASSOCIATIONS FOR RHEUMATOLOGY

CLASSIFICATION CRITERIA FOR EOSINOPHILIC GRANULOMATOSIS WITH POLYANGIITIS

CONSIDERATIONS WHEN APPLYING THESE CRITERIA

- **These classification criteria should be applied to classify a patient as having eosinophilic granulomatosis with polyangiitis when a diagnosis of small- or medium-vessel vasculitis has been made**
- **Alternate diagnoses mimicking vasculitis should be excluded prior to applying the criteria**

CLINICAL CRITERIA

Obstructive airway disease	+3
Nasal polyps	+3
Mononeuritis multiplex	+1

LABORATORY AND BIOPSY CRITERIA

Blood eosinophil count ≥ 1 ×10⁹/liter	+5
Extravascular eosinophilic-predominant inflammation on biopsy	+2
Positive test for cytoplasmic antineutrophil cytoplasmic antibodies (cANCA) or antiproteinase 3 (anti-PR3) antibodies	-3
Hematuria	-1

Sum the scores for 7 items, if present. A score of ≥ 6 is needed for classification of EOSINOPHILIC GRANULOMATOSIS WITH POLYANGIITIS.

E. Small Vessel Vasculitis

The most common types of immune complex mediated Small Vessel Vvasculitis include

E1.Hypersensitivity Vasculitis,

E2.Henoch–Schönlein Purpura (Hsp), And

E3.Cryoglobulinemic Vasculitis.

- Hypersensitivity vasculitis is most commonly idiopathic or due to a drug or infection.

HSP

- HSP presents with palpable purpura, arthritis, abdominal colic, and renal disease; skin biopsy shows leukocytoclastic vasculitis with IgA deposition in vessel walls on direct immunofluorescence.
- The classic tetrad of palpable purpura, arthritis, abdominal pain, and renal disease occurs in up to 80% of cases.
- It is most common childhood vasculitis.(aged 2-10 years)
- Adults have more severe disease with a higher frequency of progressive renal disease.
- Diagnosed on skin biopsy showing IgA vasculitis.
- The disease is generally self-limited, lasting from 6 to 16 weeks. For mild cases, supportive treatment alone may be adequate. Arthritis responds to nonsteroidal anti-inflammatory drugs (NSAIDs). Systemic glucocorticoids (prednisone 1 mg/kg per

Scanned with CamScanner

day × 2 weeks with tapering off over 2 weeks) may be used in patients with GI involvement or bleeding.

Mixed cryoglobulinemic vasculitis

- It is an immune complex-mediated small-vessel vasculitis commonly associated with chronic hepatitis C virus (HCV) infection, systemic autoimmune diseases (especially Sjögren's syndrome), and lymphoproliferative disorders.
- Palpable purpura, weakness, and arthralgias are the most common manifestations of mixed cryoglobulinemic vasculitis, but renal involvement is most closely associated with a poor prognosis.
- Rituximab (RTX) is the recommended treatment for HCV-associated cryoglobulinemic vasculitis in the setting of progressive, organ-threatening disease, particularly when used in combination with antiviral agents.

Behçet's disease

- Should be considered in any patient with recurrent orogenital ulcers (> 3 times/year) and uveitis.
- It involves vessels of all types (arteries,capillaries,veins) of all sizes of vessels (small,medium,large)
- Behçet's disease is the only vasculitis to cause pulmonary aneurysms.
- Pathergy sign (erythema of ≥ 2mm) at the site of needle sticks is characteristic of Behçet's disease.

Scanned with CamScanner

APPROACH TO FATIGABILITY (Due to anemia)

It is crucial to determine either one blood cell line, two or all cell line is affected like

- **WBC** → HX of fever
- **RBCs**→ pallor of complexion
- **Platelets**→ HX of brusibility and gums bleeds

Because each one has different differential diagnosis

P/C

Fatigability....3 months

(HOPI)ODPARAV

My patient presented with Fatigability (means lack of energy, generalised weakness and /or increased tiredness) that is gradual in onset, progressive in nature and remain persist throughout the day and there is no diurnal variation (differentiation point from **MG**). According to the patients, fatigability is aggravated by activities and improves with rest. It is associated with pallor of complexion, palpitation and SOB on exertion, However, there is no HX of recurrent Fever (rule out ↓of WBC) and easy brusibility (rule out ↓ of platelets). Patient denied HX of...

Exclude DDs

1. **Iron Deficiency Anemia**

- HX of poor diet, warm infestation, recurrent blood loss, blood in the stool, menorrhagia, multiple pregnancy, difficulty in swallowing, (plumer Vilson syndrome)

2. **Megaloblastic anaemia**

- HX of Pure Vegan Diet →HX of weakness of any part of the body , tingling sensation and memory impairment
- HX of GI surgery (stomach and ileal resection)
- HX of prolong intake of drugs like ATT(isoniazid) , metformin , MTX and antiepileptic drug
- HX of CLD →black colour stool and blood in the vomiting)
- Hypothyroidism→ cold intolerance
- Pernious anemia→ Hx of chronic greasy, diarrhea white spot on the skin and early greying of hair
- **Folic Acid Deficiency**
  - HX of ↓ folic acid blood level
  - HX of Psoriasis(silver skin lesions)
  - HX of antiepileptic medication
  - Hx of lumps & bumps (increased cell turnover that leads to ↓ Folic acid)

3. **Lead poisoning**

- HX of living in the old house, exposure to lead and chemicals and recent painting in the house

4. **Anemia of Chronic Disease**

- HX of chronic illness like TB, bronechatsis, CCF, CLD and CKD.

5. **Aplastic anemia**

Scanned with CamScanner

- HX of prolong exposure to chemical (bezen, rubber and pesticides) & radiation, drugs like Gold, MTX, antiepileptic drug and immune suppressant. HX of lumps and bumps (malignancy) , HIV and it drug ,HBV,HCV and family HX of aplastic anemia
- HX of cola colour urine in the morning **(PNH)** and joints pain and photosensitivity **(SLE)**

6. Hemolytic anemia

- Family HX of yellow discoloration of sclera and right hypochondrial pain, bones pain and leg ulcer, cola colour urine after antimalarial drug, rigors and chills after blood transfusion and heart valve replacement.

7. Multiple myeloma

- HX of back pain , pallor of complexion and polyuria

8. Malaria & mycoplasma pneumonia

- Hx of mosquito bite and dry cough

9. Bleeding disorder and anticoagulant

- There is no HX of bleeding on trivial trauma and recent use of blood thinning medication

10. Autoimmune /connective tissue disorder (SLE , RA and MCTD)

- Hx of morning stiffness of joint, photosensitivity and pain in the muscles

11. Malabsorption (see Approach to chronic diarrhea)

- Hx of chronic greasy diarrhea that is floating and foul smelling

CARE

Complications of Anemia

- Heart failure
- Angina
- Iron overload(repeated transfusions) → darkening of skin and new onset DM and joints pain
- PNH → stroke and DVT
- Pigmented Gall stones
- Dysphagia (Plummer Vinson)
- Delay growth

Ask relevant

ITP &PAM-HUGS-FOSS-TV-F

Examination

Vitals

GPE →koilonychia, clubbing, pulse, JVP, conjunctival pallor, jaundice (hemolytic anemia), glossitis, angular stomatitis, cheilosis edema and thyroid

Abdomen → hepatosplenomegaly, sternal tenderness and Para aortic lymph nodes

CVS → see murmur and signs of heart failure

Resp → examine the back of the chest for chronic illness and crackles of the heart failure

CNS → proximal myopathy, proprioception and vibration for macrocytic anemia (B12), power and reflexes for the same reason mini mental score and fundascopy

Scanned with CamScanner

VIVA OF ANEMIA

How will you investigate this patient?

- **CBC →↓ HB**, raised platelets and MCV status depend on the underlying cause
- **Peripheral smear**
  - microcytic hypochromic anemia with anisocytosis (variation in the size), poikilocytosis(variation in the shape of red cells) with target ,pencil-shaped and or cigar shaped cells (in IDA)
  - Ringed sideroblasts(Prussian blue) are pathognomonic for sideroblastic anemia anemia
  - Bite cell →G6PD
  - Sickle cell etc
- **Iron profile →**
  - serum Ferritin (< 12 ng/mL or <30ng/mL if complexion is of anemia) is the single best test to confirm iron deficiency
  - Total iron binding capacity (TIBC)→ raised while reduced in anemia of chronic disease
  - Transferrin saturation → calculated by serum iron iron /TIBC < 16% is suggestive of IDA but is less specific than ferritin measurement
- **Investigation of the causes of anemia**
  - It is depending on your case , age , gender HX and clinical finding
  - Stool R/E for ova and cyst
  - Anti-TTG
  - Upper and lower GI endoscopy etc
- **HB electrophoresis** → thalassemia
- **G6PD level**
- **Direct and indirect Coombs test**→Hemolytic anaemia's
- **Osmotic fragility test or Eosin -5-maeleimide binding test(EMA)**→ Hereditary Spherocytosis
- **Osmotic gradient ektacytometry**→ to differentiate Hereditary Spherocytosis from hereditary stomatocytosis
- **Flow cytometry (immunophenotyping) of blood** →absence of CD55 and CD 59
- **If MCV is raised** →B12 , Folic Acid , TFTs and LFTs
- **Anemia of chronic disorders**
  - LFTs→ CLD (raised bilirubin may also indicate hemolytic anemia)
  - LFTs→ CKD
  - Echo → CCF
  - ETC
- **Bone marrow biopsy , retics count**
  - May reveal aplastic anemia and various infiltrative disorders
- **Others**
  - LDH, haptoglobulin ,positive urinary hemosiderin , hemoglobinuria, raised unconjugated bilirubin , Hepcidin and CXR for atypical pneumonia

Scanned with CamScanner

What is anemia?

Anemia is ↓ in HB or HCT according to age, race and gender.

- In male anemia is confirmed when HB is <13.6 and HCT is less than 41%
- While in female anemia is defined by HB <12g/L and HCT less than 36%

How will you classify anemia?

What are the stages of iron deficiency?

Depletion of iron stores →anemia with normal MCV →anemia with ↓ MCV

Scanned with CamScanner

IRON DEFICIENCY ANEMIA (IDA)

What is the daily requirement of iron in iron deficiency anemia?

- Normally iron balance is maintained B/W absorption of 1mg/day and loss of 1mg/day .However , this balance is disturbed during pregnancy ,lactation and blood loss like heavy menstrual cycle
- RDA for non-pregnant women →15mg/day
- RDA for pregnant women →27mg /day
- RDA for male 8mg/day
- Heavy menstrual flow 2-5mg/day

How will you treat IDA?

Unless there is angina, heart failure and cerebral hypoxia, oral iron replacement is all that is needed to correct anemia. Foods rich in iron are green leafy vegetables, eggs, and meats while vit C help absorb iron.

Available forms **of oral iron** are

- Ferrous fumarate (richest iron form but intolerable)→Tab lowrate® 150/0.5mg, Marivet-F® 150 /0.5mg
- Ferrous sulphate 325mg /day→ Tab Femorate® 200mg , tab Iromed® 150/0.5 mg
- Ferrous gluconate(300mg BD with 70 mg elemental iron/day) → Tab Blomic 150/0.5 mg
- Iron supplement should be taken on empty stomach , once a day and may be taken with vitamin C to enhance it absorption

Parenteral Iron

Parenteral iron replacement is indicated in certain condition like malabsorption, chronic gut disease (IBD) and not able to tolerate oral iron and refractory anemia. Available formulation include

- Old preparation were iron dextran (outdate now due to allergic reaction and prolong infusion time)
- Iron sucrose (venofer®)→ 100mg/5ml
- Ferric Carboxymaltose complex (Ferinject® , Fercari®) →50mg/mL and 1 Vial is 10mL containing 500mg and infusion time is 15 -30 minutes
- Calculation of iron dose = (Desired HB- patient HB) ^{x} weight ^{x} 2.4+ 500

Response to treatment

- Haematocrit increased in 3 weeks and become normal in 2 months and treatment should be continued 3-6 month after normalization of HCT

What is refractory anemia?

- When HB increased less than 1mg/dL (10g/L) after 4-6 weeks of 100mg/day of elemental iron.
- It could be due to celiac disease , H-pylori gastritis(↓acid secretion) , malabsorption and hereditary iron –deficiency anemia
- Treatment is switch to parenteral iron

What are the Recent Advances?

Scanned with CamScanner

Ferric pyrophosphate citrate additive to the dialysate to replace iron loss (5-7mg/ session) in CKD patients on haemodialysis

Anemia of chronic Disease(ACD)

It may be due to the following reason

- Anemia of inflammation →IBD,RA and malignancy
- Anemia of organ failure →CKD , CLD (↓ erythropoietin &RBC mass , iron is normal except in CKD
- Anemia of older age → in 20% individual over age 85
- Clonal cytopenias of undetermined significance → may leads to MDS 1-1.5%/ year

How to differentiate b/w Iron deficiency anaemia (IDA) and Anaemia of chronic disease (ACD)?

	Ferritin	Iron	TIBC	Transferrin Saturation	Transferrin Receptor
IDA	↓	↓	↑	↓	↑
ACD	↑/Normal	↓	↓	↓	↓/Normal

Serum ferritin less than 30ng/mL indicated co existent iron deficiency anemia. It is noteworthy that diagnosis of iron deficiency on the background of anemia of inflammation where serum ferritin can be as high as 200ng/mL .Therefore, the diagnosis is made by bone marrow biopsy with iron stain .Consequently, absent iron, staining indicates iron deficiency whereas iron localized in marrow macrophage indicates anemia of chronic diseases (inflammation) but this is rarely done .Additionally , the following two are also suggestive of IDA (1) a reticulocyte HB of <28 pg or (2) a soluble of soluble serum transferrin receptor / log ferritin ratio of 1-8 while < 1 is diagnostic of anemia of chronic disease .However ,the easy way is to give oral/parenteral iron and a positive response is suggestive of IDA rather than ACD .

Treatment of ACD

Mainstay of treatment is to treat the underlying cause .Additionally, when anemia is affecting the quality of life, then we have the following treatment options

- RBC transfusion
- Parenteral erythropoietin transfusion (in IBD , RA ,chronic HCV ,HIV and CKD)

Scanned with CamScanner

THALASSEMIA

Haemoglobin	Chains
Hb A	**α2β2** (two alpha and two beta chains)
Hb A2	α2δ2 (Two alpha and two delta chains)
Hb F	α2γ2 (two alpha and two gamma chains)

Alpha –thalassemia syndrome

Numbers Of Alpha –Goblin Genes Transcribed	Syndrome	Hematocrit	MCV
4	NORMAL	Normal	normal
3	Silent carrier	Normal	normal
2	Thalassemia minor(or trait)	28-40%	60-75fL
1	Hemoglobin H disease	22-32%	60-70 fL
0	Hydrops fetalis1	<18%	<60fL

- HB electrophoresis is the investigation of choice
- Two copies of the alpha –globlin genes are located on each chromosome 16(alpha-thalassemia
- One copy of the beta –globin gene located on each chromosome 11

Beta - thalassemia syndrome

	Beta- globin Genes transcribed	Hb A	Hb A_2	Hb F	transfusions
Normal	Homozygous beta	97-99%	1-3%	<1%	none
Thalassemia minor	Heterozygous $beta^0$	80-95%	4-8%	1-5%	none
	Hetrozygous $beta^+$	80-95%	4-8%	1-5%	none
Thalassemia intermedia	Homozygous$beta^+$(mild)	0-30%	4-8%	6-10%	occasional
Thalassemia major	Homozygous $beta^0$	0%	4-10%	90-96%	Dependent
	Homozygous$beta^+$ (severe)	0-10%	4-10%	90-96%	dependent

Scanned with CamScanner

Treatment of thalassemia

- Thalassemia minor (whether alpha or beta) does not need treatment but should be identified to avoid unnecessary investigation and treatment of anemia
- Patients with Hemoglobin H should take folic acid daily (1mg/day) and avoid iron supplements and certain drugs (like sulphonamide to avoid oxidative stress)
- While beta-thalassemia major treatment is
- Transfusion to maintain HB > 10g/L
- Folic acid 5mg daily
- Splenectomy →If hypersplensim causes marked ↑in transfusion requirements or refractory symptoms
- Genetic counselling
- Allogeneic stem cell transplantation from HLA-compatible is the treatment of choice and only available curative therapy

What is the Recent Advance in thalassemia?

- Recently FDA approved **Luspatercept** for transfusion depended beta-thalassemia. It is a TGF-beta ligand trap that promotes erythriod maturation and ↓ transfusion requirements.

Anemia due to Vit B12 Deficiency

Investigations

- **Low B12 level**
- ↑ serum level of homocystine and methymalonic acid(the later may also be raised in CKD)
- CBC → ↑ MCV but normal MCV does not exclude B12 deficiency
- Peripheral smear → hyper segmented neutrophil >4
- Folate level may be normal

Treatment

Treatment consist of IM or SC injection of 100-1000mcg of vit B12 once daily for 7 days then weekly for 4 weeks followed by monthly for life . Folic acid should also be taken for several weeks concomitantly. Alternatively, once correction of the deficiency has done, oral replacement of B12 may be initiated for lifelong. CNS features like SCID, glove and stocking paresthesia, dementia and loss of reflexes, are reversible if present for less than 6 months. Monitor hypokalaemia for the first few days of treatment.

➢ If B12 and folic acid both are deficient, always initiate B12 first to avoid precipitation of SCID

Response to RX

- Retics count improve in 5-7 days while the blood picture become normal in 2 months
- If the initial response is not maintained and blood picture is dimorphic(mixed micro & macro) , the patient may need additional iron therapy

Hemolytic Anemias

I. Paroxysmal Nocturnal Haemoglobinuria

Scanned with CamScanner

- It is acquired disorder characterized by haematopoietic stem cell deficient in glycosylphophatidylinositol (GPI) that anchor many key defence molecules including CD55 and CD59 to RBCs membrane to prevent complement mediated lysis .Therefore , its absence result in intravascular haemolysis particularly in early morning

Investigation

- **Flow cytometry** (of blood erythrocytes, granulocytes, and monocytes) to demonstrate deficiency of CD55 and CD59 is the best screening test
- The FLAER assay (fluorescein-labeled proaerolysin) by flow cytometry is more sensitive.
- **Bone marrows Biopsy finding are** variable and may show either generalized hypoplasia or erythroid hyperplasia or both. The bone marrow karyotype may be other normal or may reveals a clonal abnormality
- **Serum LDH** is characteristically qua elevated.
- **CBC** Iron deficiency is commonly present, related to chronic iron loss
- **Urine** hemosiderin is also a useful test

Treatment

- Patients with mild disease do not requiring treatment and should be monitor only .while in other management is supportive with transfusion, folate supplements, prophylaxis, and treatment of thrombosis.
- In patients with severe hemolysis or thrombosis (or both), treatment with eculizumab is indicated (a humanized monoclonal antibody against complement protein C5 given ray 2 weeks). Binding of eculizumab to C5 prevents its cleavage so the membrane attack complex cannot attack the red cell. However, there is Increases the risk of Neisseria meningitidis infection and therefore patient should be vaccinated against this bug. . Ravilizumab is a longer-acting version of propter eculizimab, it is given every 8 weeks
- In severe cases and in those occurring in the setting of myelodysplasia and previous aplastic anemia, allogeneic hematopoietic stem cell transplantation may be curative
- Iron replacement if iron deficiency is present,
- Surprisingly, corticosteroids are effective in ↓ hemolysis.

Prognosis→ 10-15 years after diagnosis and primary cause of death is thrombosis

II. Glucose-6 Phosphate Dehydrogenase Deficiency (G6PD)

- X-liked recessive disorder and with over 400 subtypes. patient are asymptomatic and haemolysis may occours periodically precipitated by infection and or drugs (oxidative stress)

Pathophysiology

- ↓G6PD →↓glutathione→increased red cell susceptibility to oxidative stress
- The hemolytic anaemia is non-immune and therefore the direct antiglobulin test (DAT) negative

Scanned with CamScanner

Investigation

- **Peripheral blood cell smear** →reveals a small number of "bite" cells or "blister" cells. This is precipitated hemoglobin aggregates (ie, Heinz bodies) by the splenic macrophages. Heinz bodies may be demonstrated by staining a peripheral blood smear with cresyl violet, as it is visible on the usual Wright-Giemsa-stain).
- **Specific enzyme assays for** G6PD reveal a low level but may be falsely normal if they are performed during or shortly after a hemolytic episode. Therefore, the enzyme assays should be repeated weeks after hemolysis has resolved. In severe cases of G6PD deficiency, enzyme levels are always low.
- **LFTs**→ and increased serum indirect bilirubin.
- **CBC**→ During episodes of hemolysis, the hemoglobin rarely falls below 8 g/dL and there may be immature cell on smear

What are the drugs that causes haemolysis

Antimalarial like primaquine, rasburicase, nitrofuraontion, sulphonamide (like trimethoprim/sulfamethoxazole, sulfadiazine and sulfonylurea), pegloticase, and quinolones, dapson and methylene blue. Other medications, such as chloroquine, quinine, high-dose aspirin, and isoniazid, are also reported to cause haemolysis. Haemolysis typically occours 24-72 hours after ingestion with resolution within 4-7 days.

What are the safe drugs?

- Penicillin
- Cephalosporins
- Macrolide
- Tetracycline
- And trimethoprim (but not sulfamethoxazole)

Treatment No treatment is required except to avoid oxidative stresses in the form of an infection, oxidative drug and fava beans.

Scanned with CamScanner

Comparison of G6PD deficiency and hereditary spherocytosis

	G6PD Deficiency	Hereditary Spherocytosis
Gender	Male (X-linked recessive)	Male + female (autosomal dominant)
Ethnicity	African + Mediterranean descent	Northern European descent
Typical history	Neonatal jaundice Infection/drugs precipitate haemolysis Gallstones	Neonatal jaundice Chronic symptoms although haemolytic crises may be precipitated by infection Gallstones Splenomegaly is common
Blood film	Heinz bodies	Spherocytes (round, lack of central pallor
Diagnostic test	Measure enzyme activity of G6PD	Osmotic fragility test

III. Sickle cell anemia

- Autosomal recessive disorder caused by the substitution of glutamic acid by valine at position 6 of the beta chain
- Major types are following
  - Sickle cell trait→ heterozygous (HbAS)
  - Sickle cell disease→ homozygous (HbSS). Other rare form are
  - HbSC (sickle –Haemoglobin C disease)
  - HbS/β^+(sickle –beta –plus thalassemia
  - HbS/β0(sickle-beta-zero thalassemia)

Investigation

- Sickle cell anemia is confirmed by Hb electrophoresis→ HbS
- The peripheral blood smear reveals sickled cells (consisting 5-50% of red cells. Other findings are nucleated red blood cells, and Howell-Jolly bodies and target cells(due to hyposplenism)
- Indirect bilirubin levels are high due to chronic haemolysis.

Complications

There are 4 main types of crises

Thrombotic crises,

- It is also known as painful crises or vaso-occlusive crises. It is precipitated by infection, dehydration, deoxygenation acidosis, cold temperatures, extreme exercise, and stress.

Scanned with CamScanner

- Infarcts occur in various organs including the bones eg. avascular necrosis of hip, hand, foot syndrome in children, lungs, spleen and brain

Sequestration crises

- sickling within organs such as the spleen or lungs causes pooling of blood with worsening of the anaemia
- acute chest syndrome characterized by dyspnoea, chest pain, pulmonary infiltrates, low pO2 - the most common cause of death after childhood
- Stroke about →5-10% of sickle cell patients will suffer a stroke, usually during childhood. The risk can be predicted by transcranial Doppler measurement of middle cerebral artery (MCA) flow rate and if the doppler velocity is abnormal, (≥200cm/s. then prompt institution of a prophylactic transfusion should be considered to prevent stroke (in HbSS patients), to suppress HbS production, and to maintain HbS level < 30%. Treatment of stroke once occurred is exchange transfusion programme

Aplastic crises

- Caused by infection with parvovirus-19 .Sudden fall in haemoglobin without an appropriate ↑ reticulocytosis.The condition is seif-limited, with bone marrow recovery occurring in 7-10 days, followed by brisk reticulocytosis.

Haemolytic crises

- it is Rare .The anaemia associated with sickle cell disease is usually only symptomatic below 70 g/L as oxygen is released more readily from erythrocytes. Remember, patients with sickle cell tend to run with a Hb between 70-90 g/L normally

The anemia of SC is usually a chronic, reasonably well compensated hemolytic anemia.

What is acute chest syndrome?

It is defined as an acute illness characterized by fever and/or respiratory symptoms, accompanied by a new pulmonary infiltrate on chest X-ray'.

Management

- Oxygen therapy to maintain saturations > 95%
- Intravenous fluids
- Adequate pain relief
- Incentive spirometery in all patients presenting with rib or chest pain
- Antibiotics with cover for atypical organisms
- Blood transfusion:
- A haematologist will make a decision as to whether a simple or exchange transfusion is necessary.

Hb target of 10-11g/dL in either instance

Once patient is recovered from acute infection then

All adults who have hyposplenism should have following vaccination

- Yearly influenza vaccine.
- Pneumococcal C vaccine, (adults, and children over 2 years) repeated every five years.

Scanned with CamScanner

- Haemophilus influenzae type b; if not already given as part of childhood immunization.
- Conjugated meningococcal C vaccine; if not already given as part of childhood immunization.
- Meningococcal ACWY vaccine; if travelling to areas with high risk of meningitis.

- Patients with sickle cell disease are prone to infections with encapsulated organisms (Streptococcus pneumonaie Haemophilus influenzae and Neisseria meningitidis) because of their asplenic state.

To combat these infections, patients with homozygous sickle cell disease should be on lifelong penicillin and be vaccinated against these organisms

.

Treatment

- Supportive care is the mainstay of treatment for sickle cell anemia. Patients should be given folic acid supplementation and transfusions for aplastic or hemolytic crises. When acute painful episodes occur, precipitating factors identified and treated. Hydroxyurea and L-glutamine reduce hospitalizations for acute pain.
- Allogeneic hematopoietic stem cell transplantation before the onset of end-organ dam- age, can cure more than 80% of children with sickle cell anemia who have suitable HLA-matched donors while Transplantation remains investigational in adults
- Hydroxyurea (500-750 mg orally daily) ↓the frequency of painful crises. It also improves overall survival and quality of life .likewise the use of omega-3 fatty acid may also reduce vaso-occlusive episodes and reduce transfusion needs in patients with sickle cell anemia. L-glutamine has been also shown to reduce sickle pain crises and acute chest syndrome.
- **Crizanlizumab-tmca** (a monoclonal anti-body) reduces vaso-occlusive episode by 50%
- **Voxelotor** (HB- Oxygen affinity modulator **MOA** → dose depended inhibition of HbS polymerization) It increases the hemoglobin in HbSS patients age≥ 12
- Indications for exchange transfusions are severe or intractable acute vaso-occlusive crises, acute chest syndrome, priapism, and stroke
- Iron chelation is indicated for those on chronic transfusion therapy to avoid iron overload complications.

Prognosis

- 40-50 years life expectancy

Scanned with CamScanner

Causes of Haemolytic Anaemia	
Inherited **1) Red cell membrane defect** • Hereditary spherocytosis • Hereditary elliptocyptosis **2) Haemoglobin abnormalities** • Thalassemia • Sickle cell disease **3) Metabolic defects** • Glucose - 6 – phosphate dehydrogenase deficiency • Pyruvate kinase deficiency • Pyrimidine kinase deficiency **4) Acquired** **Autoimmune** • warm • cold **Alloimmune** • haemolytic transfusion reaction • Haemolytic disease of the new-born • After allogeneic bone marrow or organ transplation • Drug-induced	**Non-immune** **1 Acquired membrane defects** • paroxysmal nocturnal Haemoglobinuria **2 Mechanical** • Microangiophatic Haemolytic o anaemia • Valve Prosthesis • March Haemoglobinuria **3 Secondary to systemic disease** –Renal and liver failure –miscellaneous section **4 Miscellaneous** • Infections like malaria and mycoplasma • Clostriduim perfrigens (welchii), generalized sepsis • Drugs and chemical causing damage to the red cell membrane are oxidative haemolysis • Hypersplensim • Burns

IV. Autoimmune Hemolytic Anemia (AIHA)

- Autoimmune haemolytic anaemia (AIHA) may be divided in to 'warm' and 'cold' types, according to at what temperature the antibodies best cause haemolysis. It is most commonly idiopathic but may be secondary to a lymphoproliferative disorder, infection, or drugs.

➢ Warm AIHA

- In warm AIHA the antibody, usually IgG causes hemolysis at body temperature and hemolysis tends to occur in extravascular sites, like spleen.

• Causes of warm AIHA

- autoimmune disease like SLE , however SLE can rarely be associated with a mixed-type AIHA
- neoplasia: e.g. lymphoma, CLL
- Drugs: e.g. methyldopa, Penicillin, Cephalosporins, levodopa, NSAIDs and Quinidine

Investigation

- **CBC** → ↓ HB of variable degree & ↓ platelets (as part of Evans syndrome)
- **Peripheral Smear** → Reticulocytosis, spherocytes, and nucleated red blood cells

Scanned with CamScanner

- **LFTs→** the serum indirect bilirubin is increased and the haptoglobin is low.
- **Coombs tests→ investigation of choice**
  - The direct anti- globulin (Coombs) test (DAT) is performed by mixing the patient's red blood cells with the Coombs reagent and looking for agglutination, which indicates the presence of anti- body or complement or both on the red blood cell surface. It is positive in 90% cases of autoimmune hemolytic anemia
  - The indirect antiglobulin (Coombs) test is performed by mixing the patient's serum with a panel of type O red blood cells. After incubation of the test serum and panel red blood cells, the Coombs reagent is added. Agglutination in this system indicates the presence of free antibody in the patient's serum. Indirect test may or may not be positive. A positive test indicates the presence of a large amount body that has saturated binding sites on the RBCs and consequently appears in the serum.

Treatment

Initial treatment is prednisone (1-2 mg/kg/day orally) in divided doses. If prednisone is ineffective or if the disease relapse on tapering dose, splenectomy should be considered, which may cure the illness. Patients who are refractory to prednisone and splenectomy may be with rituximab, (375 mg/m² intravenously) weekly for 4 weeks. Additionally, rituximab may also is used in conjunction with corticosteroids as initial therapy in patients with severe disease. In severe cases transfusion should be performed under the strict observation of haematologist .therapeutic plasmapheresis should be performed early in management to remove autoantibodies

Danazol, 400-800 mg/day orally, is less effective (than in ITP) but is well suited for long-term use because of its low toxicity. Immunosuppressive agents, like cyclophosphamide, azathioprine, mycophenolate mofetil, or cyclosporine, may also be used. Patients who are at risk of folate deficiency due to increased metabolic demands and all should receive folic acid replacement therapy. High-dose intravenous immune globulin (1 g/kg daily for 2 days) may be effective in controlling hemolysis. However, the effect is short-lived (1-3 weeks). Treatment of the underlying disorder like lymphoproliferative disorder will also treat the anemia

➢ Cold AIHA

The antibody in cold AIHA is usually IgM and causes haemolysis best at 4 C°. Haemolysis is mediated by complement and is predominantly intravascular.

Causes of cold AIHA

- neoplasia: e.g. lymphoma)
- infections: e.g. mycoplasma, EBV

Secondary cold agglutinin disease typically presents with anaemia and haemoglobinuria due to intravascular haemolysis two to three weeks following infection such as

- Mycoplasma pneumonaie
- Viruses (EBV, CMV, etc)
- Legionnaires' disease
- Malaria → best diagnostic test →

Scanned with CamScanner

- Features may include symptoms of Raynaud's, low back pain and dark-colour urine and acrocyanosis

Investigations

- **CBC** →↓HB anemia with reticulocytosis rarely spherocytes
- **Peripheral smear** → The blood smear made at room temperature shows agglutinated red blood cells (there is no agglutination on a blood smear made at body temperature)
- **Coombs test** →The direct antiglobulin (Coombs) test will be positive for complement only.
- **Electrophoresis**→ Monoclonal IgM is often found on serum protein electrophoresis and confirmed by serum immune electrophoresis.
- **LFTs** →There is indirect hyperbilirubenemia and the haptoglobin is low during periods of hemolysis

Treatment

Treatment is mostly symptomatic like avoiding exposure to cold. Splenectomy and prednisone are ineffective (except when associated with a lymphoproliferative disorder) since hemolysis takes place the liver and blood stream. Rituximab is the treatment of choice (dose a 375 mg/m³ intravenously weekly for 4 weeks). Relapses may be re-treated similarly. High- dose immunoglobulin intravenous (2 g/kg) may be effective temporarily, but it is rarely used because of the high and short duration of benefit. Patients with severe disease may be treated with cytotoxic agents, such as bendamustine (plus rituximab), cyclophosphamide, fludarabine, or bortezomib, or with immunosuppressive agents, such as cyclosporine. As in warm AIHA, it may be difficult to find compatible blood for transfusion. Red blood cells should be transfused under strict guidance of a haematologist whenever indicated

	WARM AIHA	COLD AIHA
Definition	haemolysis best at body temperature 37 °c	Haemolysis best at 4 deg c
Antibody	IgG	IgM
Site Of haemolysis	extra vascular(spleen)	Intravascular
Direct combs test	Strongly positive	Positive
Causes	autoimmune →SLE neoplasia→ lymphoma, CLL Drugs → methyldopa	neoplasia→ lymphoma Infection →mycoplasma EBV
Treatment	Steroids, immunosuppression and splenectomy	Respond less to steroid

Scanned with CamScanner

VI. Aplastic Anemias

Anemia or pancytopenia without bone tenderness, hepatosplenomegaly and lymphadenopathy should raise the suspicion of aplastic anemia

Investigation

- **CBC→** Pancytopenia. However, early stage of aplastic anemia, only one or two cell lines may be reduced.
- **Peripheral smear →** mild macrocytosis, neutrophils, and platelets are reduced in number, and no immature or abnormal forms are seen on the blood smear. The retics counts are low
- **Bone marrow & trephine biopsy →** hypocellularity

Causes of Secondary Aplastic Anemia
Autoimmune:→ idiopathic, SLE
Chemotherapy agents and radiation
Toxin→ benzene, toluene, insecticides, carbamates and organophosphate
Medication→ chloramphenicol, gold salts, sulphonamides,
Phenytoin, carbamazepine, quinacrine, carbimazole and azathioprine
post-viral hepatitis (viral agent unknown)
Non –hepatitis viruses (EBW, parvovirus , CWM, echovirus 3,)
Pregnancy
Paroxysmal nocturnal hemoglobinuria
Malignancy: large granular lymphocytic leukemia

Causes of pancytopenia
Primary bone marrow disorder
Aplastic anemia
Myelodysplasia
Acute leukemia
Chronic idiopathic mylofibrosis
Infiltrative disease: lymphoma , myeloma, carcinoma, hairy cell, leukemia, etc
Non- primary bone marrow disorder
Hypersplensim (with or without portal hypertension)
SLE
Infection: tuberculosis , HIV, Leishmaniasis , brucellosis, CMV,
Parvovirus B19
Nutritional deficiency (↓B12)
Medication as mentioned above
Cytotoxic chemotherapy
Ionizing radiation

Scanned with CamScanner

Camitta Criteria for aplastic anemia

Severe aplastic anemia (SAA)

- Marrow cellularity < 25% (or 25-50% with <30% residual haematopoietic cells), pulse at least two of following
- Neutrophils<0.5x10^9/L
  Platelets <20x10^9/L
- Reticulocyte count <20x10^9/L

Very severe aplastic anemia (VSAA)

- As for SAA but neutrophils <0.2x10^9/L

Non-severe Aplastic anemia (NSAA)

- AA not fulfilling the criteria for SAA or VSAA

Treatment

Mild idiopathic aplastic anemia may be treated with supportive care, like erythropoietic agents (epoetin→ 50-100 units thrice/week or darbepoetin) or myeloid agents (filgrastin→ 5ug/kg/day SC), or both. Red blood cell transfusions and platelet transfusions are given when indicated, and antibiotics are used to treat infections.

Severe aplastic anemia (as defined by camitta criteria) the treatment of choice for young adults (age < 40 years) who have an HLA- matched sibling is allogeneic bone marrow transplantation (curative). Additionally, Children or young adults may also benefit from unrelated donor allografts. However, due to risks associated with unrelated donor this treatment is usually reserved for patients who have not responded to immunosuppressive therapy.

For adults over age 40 years or those without HLA- matched donors, the treatment of choice for severe idiopathic aplastic anemia is immunosuppression with equine antithymocyte globulin (ATG) combined with cyclosporine. A proven regimen is equine ATG 40 mg/kg/day intravenously for 4 days in combination with cyclosporine, 6 mg/kg orally twice daily. Eltrombopag, a thrombopoietin mimetic, is now being added to ATG plus cyclosporine with responses as high as 90%. ATG should be used in combination with corticosteroids (prednisone or methylprednisolone 1-2 mg/kg/day orally for 1 week followed by a taper over 2 weeks) to avoid ATG infusion reactions and serum sickness. Responses usually occours in 1-3 months and are commonly partial, but the blood counts rise high enough to give patients a safe and transfusion-free life. The full benefit of immunosuppression is generally assessed at 4 months post-equine ATG. Cyclosporine and eltrombopag are maintained at full doses for 6 months and then stopped in responding patients.

Androgens (such as fluoxymesterone 10-20 mg/day orally in divided doses or Danazol 200 mg orally twice daily) have been widely used in the past, may also be considered in mild cases.

Scanned with CamScanner

For secondary aplastic anemia the underlying cause should be treated or culprit agents removed if possible otherwise the management is same as for idiopathic aplastic anemia

Prognosis

Rapidly fatal if untreated

Miscellaneous points

- Blood storage temperature
  - Whole blood → <4C° Life span 30-40 days
  - Platelets → 20C° .1 bag raised 10K while 1 mega unit raised 60 K platelets
  - FFPs→ half-life many years
- Corrected Retics = $\frac{\text{HCT of patients} \times \text{Retics \%}}{\text{Average normal HCT}}$

Scanned with CamScanner

APPROACH TO LUMPS AND BUMPS (Due to Lymphoma)

- Pancytopenia without lumps &bumps → proceed like aplastic anemia
- Pancytopenia with lumps & bumps → proceed as follow

P/C Lumps &Bumps -------3months

HOPI (ODPARA-V)

According to the patients, he presented with lumps & bumps that is gradual in onset progressive in nature and 3 months in duration. According to the patients, he first noticed it in the right cervical region that was 2-3 in numbers, pea sized, painless and soft in consistency; however, with time it was progressively enlarged, increased in numbers and involved other areas of body like armpit, posterior cervical area and inguinal regions. Lumps and bumps are associated with ↓ appetite, significant unintentional weight loss of 8kg, and fever for the same duration. There is no HX of pallor of complexion, yellow discoloration of sclera, skin brusibility and bleeding from any orifice of body. However, Patient denied HX of

- In HOPI you must tell whether it is probably a case of single line blood disorder or bicytopenia and or pancytopenia (recurrent fever , pallor of complexion and easy brusibility or bleeding from anybody orifice)

Now exclude DDs

- **Lymphoma** →long case here , see care
- **Local pathology** → ENT& dental infection
- **Leukemia** → patient denied HX of blood malignancy
- **Disseminated TB** → patient denied HX of blood stained cough , HX of contact with TB patient
- **HIV** →there is no HX of high risk sexual behaviour and IV drug abuse
- **Brucellosis**→ No HX of animal contact and unpasteurized milk ingestion
- **EPV,CMV and toxoplasmosis** →HX of sore throat , redness of eyes and cat contact respectively
- **Sarcoidosis** →HX of dry cough and painful shin nodules
- **Drug induced** →there is no Hx of prolong intake of phenytoin ,carbamazepine , allopurinol and sulphonamide
- **Autoimmune disorder like SLE ,RA, adult onset still disease and sjogren syndrome**→ No HX of joints , oral ulcer and skin rash

CARE /RECA

There is HX of exposure to hair dye and pesticides .However, patient denied HX of exposure to radiation, chemo, chronic viral infection, family HX of malignancy, smoking and alcoholism and joints pain, skin rash.

- Risk and aetiology of leukemia and lymphoma **are same**

Complications

- Gout (due to raised uric acid) →HX of joints pain and body aches
- Nephrotic syndrome (due MPGN)→ periorbital swelling and blood in the urine

Scanned with CamScanner

- Autoimmune hemolytic anemia →jaundice
- DVT/PE
- Stroke
- Hyperviscosity→ blurring of vision and epistaxis
- Spastic Paraparesis (due to Mets)→ weakness in limbs
- Metastatic disease from head to toe
- Dysphagia & dysphonia
- SVCO→ face congestion and swelling
- Heaviness in R&L hypochondrium
- Pruritus
- Symptoms like pruritus ,skin rash ,facial flushing ,back pain and fatigability may points toward hodgkin lymphoma but can also occours in non-Hodgkin lymphoma

Ask relevant

ITP and

PAM-HUGS-FOSS-TV-F

Examination scheme

Vitals

GPE → general look ,anemia, scratch marks, epitrochlear nodes (must to do) and other group of lymph nodes (look for site, number , size , consistency , mobility , tenderness) , JVP , jaundice , herpetic rash (immunocompromised state) and bony tenderness

Abdomen → Hepatosplenomegaly, Para aortic lymph nodes and ascites and

Resp → examine for pleural effusion, collapse of lung (due to lymphadenopathy) and cavitation

CVS→ always look for signs of superior vena cava obstruction, pericardial effusion (muffled heart sound, JVP and low BP triad of cardiac tamponade), and orthostatic hypotension due to Mets to adrenal (check in short short cases as well)

CNS → look for cord compression signs (UMN sign) in lower limbs cranial nerves palsies) and finally fundascopy (hemorrhage)

Scanned with CamScanner

VIVA OF LYMPHOMA

How will you investigate this patient?

- **CBC** →↓ cells line or normal, however, anemia and lymphopenia if present are poor prognostic factors
- **Peripheral smear** → mostly normal even in advanced disease
- **ESR** → may be raised
- **RFTs**→ to check before treatment
- **LDH** → raised level is poor prognostic factor
- **LFTs**→ may be abnormal due to infiltration , hemolytic anemia or obstructive pattern caused by enlarged nodes at the porta hepatis
- **ECHO→ to check before treatment**
- **Chest-X-ray** → mediastinal mass
- **CT-chest , abdomen and pelvis** → to stage the disease , a single mass >10cm is poor prognostic factor
- **PET-Scan** →for accurate staging and to monitor response to treatment
- **Bone marrow biopsy** → for staging .May be normal or may shows paratrabecular monoclonal lymphoid aggregate in case of involvement
- **Lymph node Biopsy(FNAC & or excisional)** → diagnosis is made by lymph node biopsy or involved extranodal tissue .it also help in classification of the disease

What are the two major types of lymphoma?

The two major types are Hodgkin and non-Hodgkin lymphoma

What are the conditions/disorders beside Hodgkin lymphoma where Reed-Sternberg Cell Found?

- Infectious mononucleosis
- Malignant melanoma
- Burkit lymphoma and
- Breast cancer

Scanned with CamScanner

How will you differentiate Hodgkin and non-hodgkin lymphoma?

lymph node involvement	Usually localized to single axial group	Peripheral lymph node involvement
Mesenteric lymph node and waldeyer ring	Rarely involved	Commonly involved
Lymph node spread	Orderly spread by contiguity	Noncontagious hemtogenous spread
Consistency	Rubbery	Variegated or firm
Extranodal	Less common	More common
Involvement systemic features	Common	Less common
Pel-Ebstein fever	My occur	Does not occur
Pruritis	Common	Less common
Reed-Sternberg cell	Present	Absent
Age	Young age	Older age
Prognosis	High cure rate	Low cure rate

I) Hodgkin Lymphoma

The Hodgkin lymphoma is derived from B-lymphocytes of germinal center origin characterized by the presence of Reed-Sternberg cell

What features are more suggestive of Hodgkin Lymphoma?

- Bimodal (20-30 and 50-70 age group)
- B symptoms like pruritus , weight loss and drenching night sweats
- No visceromegaly
- No waldeyer ring and peripheral lymph nodes like epitrochlear lymph nodes
- Multiple discrete rubbery painless lymph nodes in both side of the neck and axilla
- While the opposite features are suggestive of non-Hodgkin lymphoma

What is the WHO classification of Hodgkin Lymphoma?

- **Nodular sclerosing** → most common(70%) having good prognosis

Scanned with CamScanner

- **Mixed cellularity**→ 2nd most common(20%) and having large number of Reed-Sternberg cell and having good prognosis
- **Lymphocyte predominant** → best prognosis (5%)
- **Lymphocyte depleted**→ worst prognosis (rare)

The above mention types are also called classical lymphoma while Non-classic Hodgkin lymphoma (nodular lymphocyte predominant) lack reed-Sternberg cells

What are the poor prognostic factors?

- Weight loss >10% in the last 6 months
- Night sweats
- Fever >38C
- Stage IV disease
- Age >45 and male gender
- A mass > 10 cm in size
- Albumin <40g/l
- CBC showing
  - WBC>15,000/l
  - HB<10.5g/dl
  - Lymphocytes <600/l or <8%

What is ann-Arbor staging of Hodgkin lymphoma?

- **Stage I**→ involvement of single lymph node region(I) or extra lymphatic site(I_E)
- **Stage II**→ involvement of ≥ 2 lymph nodes(II)/regions/extra lymphatic site on the same side (above or below) of diaphragm(II_E)
- **Stage III** →involvement of lymph nodes on both sides of diaphragm (with (III_E) or without(III) localized extralymphatic involvement or involvement of the spleen (III_s) or both (III_{SE})
  - Lymphoma with splenomegaly → stage III
- **Stage IV**→ Spread beyond lymph nodes like involvement of ≥1 extra

Each stage is sub classified as

A→ no systemic symptoms other than than pruritus

B→ fever >38C, drenching night sweats and weight loss of > 10%

What is generalized lymphadenopathy?

When ≥3 non-contiguous lymph node areas are involved is called generalized lymphadenopathy

What are the patterns of fever in lymphoma?

There is no pathognomonic pattern .Fever is usually low grade without rigor & chills. Classically Pel-Ebstein fever occours in Hodgkin disease. Additionally, fever pattern may be remittent, continuous, swinging fever with sweating in lymphoma

What is Pel-Ebstein fever?

Scanned with CamScanner

It is a cyclical or periodic fever where several days or weeks of fever alternate with afebrile period.

What are the causes of Pel-Ebstein fever?

- Hodgkin disease
- Brucellosis
- Renal carcinoma

What are the causes of anemia in lymphoma?

- Ineffective erythropoiesis due to bone marrow infiltration)
- Hemolysis (autoimmune hemolytic anemia)
- Hypersplensim
- Hemodilution

What are the causes of jaundice in lymphoma?

- Hepatic involvement
- Compression at porta hepatis by lymph nodes
- Hepatitis due to repeated blood transfusion
- Hemolysis (autoimmune)

How will you treat this patient?

Chemotherapy is the mainstay of treatment for Hodgkin lymphoma, and ABVD (**doxorubicin**→ (cardio toxicity), **bleomycin**→ (Pulmonary fibrosis), **vinblastine**→ (peripheral neuropathy), **dacarbazine**→ alopecia, photosensitivity and metallic taste) is the first-line regimen.

Low risk patients

Low-risk patients are those with stage I or II disease without bulky lymphadenopathy or evidence of systemic inflammation. They are best managed with combination of short-course (2-3 courses) ABVD regimen and involved nodal radiotherapy (20 Gy INRT), but INRT can be eliminated for those with an early negative PET/CT scan.

High-risk patients

High-risk patients are those with stage III or IV disease or with stage II disease and a large mediastinal or other bulky mass or systemic inflammation.

These patients are treated with ABVD chemotherapy for six cycles. Pulmonary toxicity can occur following either chemotherapy (bleomycin) or radiation (INRT) and should be treated aggressively in these patients, as it can lead to permanent fibrosis and death. Patients with negative interim PET/CT scan after two cycles of chemotherapy may have bleomycin eliminated from their treatment (using just AVD).

The substitution of the antibody-drug conjugate brentuximab vedotin (anti CD30 on reed-Sternberg cells) for bleomycin (AAVD) is superior in progression-free survival to ABV but with no mortality benefit. The more intense regimen, BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone), is associated with increased toxicity and is reserved for patients with activity on an interim PET/CT after starting ABVD or AAVD for both low risk and high risk patients .

Scanned with CamScanner

Patients with classic Hodgkin lymphoma relapsing after initial treatment are treatable with high-dose chemotherapy and autologous hematopoietic stem cell transplantation. This offers a 35-50% chance of cure when disease is still chemotherapy responsive. Brentuximab vedotin has shown excellent activity in patients relapsing after autologous stem cell transplantation and is FDA-approved for this indication. Additionally, immune checkpoint inhibition with Nivolumab or Pembrolizumab (by PD1 blockade) has shown remarkable activity for patients with relapsed or refractory disease.

Prognosis

The cure rate 15 -75%, if 0-2 risk factors are present and 55% when ≥3 risk features are present. The prognosis of patients with stage IA or IIA disease is excellent, with 10-year survival rates in excess of 90%. Patients with advanced disease (stage III or IV) have 10-year survival rates of 50-60%. Non-classic Hodgkin lymphoma (nodular lymphocyte predominant) is highly curable with radiotherapy alone for early-stage disease; however, for advanced disease - it is characterized by long survival with multiple relapses after chemo or anti-CD20 (rituximab) therapy

II) Non –Hodgkin Lymphoma(NHL)

It includes any type of lymphoma except Hodgkin's lymphoma and most of NHL is of B cell phenotype few are T cell origin.

What is Waldeyer Ring?

It is the ring of lymphoid tissue within the oral cavity and consists of

- Adenoids above
- Lingual tonsils below
- Faucial tonsil on both sides

Investigation (specific to NHL)

- Immunophenotyping of the surface antigen of blood nodal tissue or bone marrow →to differentiate B cell and T cell
- Cytogenetic analysis (FISH)→ to detect chromosomal translocation(c-MYC)
- Electrophoresis →for immunoglobulin determination (IgG &IgM) to monitor treatment response
- HIV → it is a risk factor for lymphoma
- Screening for HBV and HCV infection → to prevent flare up during treatment with rituximab

Treatment

Treatment depend on the type of tumours weather indolent or aggressive

Indolent lymphomas

The most common lymphomas in this subgroup are

- follicular lymphoma → t(14:18) with bcl-2 overexpression
- marginal zone lymphomas(MALToma) → t(1:14)
- Small lymphocytic lymphoma

Scanned with CamScanner

The treatment of indolent lymphomas depends on the stage of disease and the clinical status of the patient. Asymptomatic patients may not require treatment and managed by wait and watching .Indication of treatment are marked systemic symptoms, lymphadenopathy ,causing discomfort or disfigurement ,bone marrow failure and compression syndrome . Patients who have limited disease with only one or two contiguous abnormal lymph node groups and may be treated with localized irradiation. However, most patients (85%) with indolent lymphoma have advanced disease at the time of diagnosis and therefore are not curable.

Treatment with rituximab (375 mg/m² IV weekly for 4 weeks) is used either alone or in combination with chemotherapy and may be the only therapy to affect overall survival. Rituximab is added to the famous chemotherapy regimens including bendamustine; cyclophosphamide, vincristine, and prednisone **(R-CVP);** and cyclophosphamide, doxorubicin, vincristine, and prednisone **(R-CHOP)**. Additionally, lenalidomide in combination with rituximab is an alternative option with similar outcomes to chemotherapy.

Following each treatment, patients will experience a relapse at shorter intervals. Some patients will have temporary spontaneous remissions.

Patients with mucosa-associated lymphoid tumours of the stomach (MALT lymphoma) may be treated by H-pylori eradication therapy with endoscopic monitoring periodically .Additionally; if the tumour is confined to, the stomach can also be cured with whole stomach radiotherapy. While MALToma of the spleen are usually associated with hepatitis, C and it may resolve with HCV treatment

Patients with aggressive low-grade lymphomas may be candidates for allogeneic stem transplantation with cure. However, the role of autologous hematopoietic stem cell transplantation remain uncertain

Aggressive lymphoma

This includes

- Diffuse large B-cell lymphoma → most common adult lymphoma t(3:4)
- High-grade lymphoma
- Mantle Cell lymphoma t(11:18)
- Highly aggressive lymphoma (Burkitt due to EBV t(8:14) or lymphoblastic)
- Peripheral T-cell lymphoma

Poor prognostic factors

- Age>60
- Raised LDH
- Stage III &IV
- >1 extranodal involvement
- Poor performance status

Diffuse large B-cell lymphoma Patients with diffuse large B-cell lymphoma are treated with 6 cycle's chemotherapy such as R-CHOP. Involved nodal radiotherapy (INRT) may be indicated for

Scanned with CamScanner

patients with bulky or extranodal disease. About 25% of patients with diffuse large B-cell lymphoma are "double-protein expressors" with overex- ression of MYC and BCL2. While the outcomes with **R-CHOP** are inferior, no definitive alternative treatment recommendations made so far **High-grade lymphoma** with chromosomal translocations affecting MYC like t(8;14), and BCL2, such as t(14;18), are called double-hit lymphoma, and has very aggressive course. These Patients are better managed with dose-adjusted R-EPOCH as first line treatment.

Patients with diffuse large B-cell lymphoma or high- grade lymphoma who relapse after initial chemotherapy can still be cured by autologous hematopoietic stem cell transplantation if the disease remains responsive to Chemo. Patients who do not respond to second-line chemotherapy, for them the the treatment of choice is either axicabtagene ciloleucel or tisagenlecleucel (chimeric antigen receptor T-cell therapy targeting CD19) which produces durable complete response (40%).

Mantle cell lymphoma (being mantle→ insane) is not responsive to standard immunochemotherapy regimens. Intensive initial immunochemotherapy including autologous hematopoietic stem cell transplantation improve out- comes. Ibrutinib and acalabrutinib (BTK inhibitors) are indicated in relapsed or refractory patients with mantle cell lymphoma. Brexucabtagene autoleucel (Chimeric antigen receptor T-cell) has excellent response in patients whose disease progresses after treatment with BTK inhibitors. Reduced-intensity allogeneic stem cell transplantation offers curative potential for selected patient.

Primary central nervous system lymphoma, for such patients repeated cycles of high dose intravenous methotrexate with rituximab in early stage, yields better results than whole-brain radiation and with less advser effect like cognitive impairment.

Highly aggressive lymphomas (Burkit →important for exam), lymphoblastic) require urgent, intense, cyclic chemothetherapy similar to that given for ALL V-DAP regimen (Vincristine, Daunorubicin, Asparginase and Prednisolone) and they also require intrathecal chemotherapy as central nervous system prophylaxis

Peripheral T-cell lymphoma mostly has advanced stage nodal and extranodal disease at presentation and less responsive to chemo compared to other aggressive B- cell lymphoma .Therefore, autologous stem cell transplantation is indicated as first line therapy. Brentuximab vedotin has significant activity in patients with CD30 positive peripheral T- cell lymphoma such as anaplastic large cell lymphoma.

Prognosis

Indolent lymphomas→ median survival is 10-15 years

Aggressive lymphoma

- Low risk patient (zero risk factors) cure rate is >80%
- High risk patient (≥4 risk factors) cure rate is <50%

Scanned with CamScanner

APPROACH TO MASS/HEAVINESS IN LEFT HYPOCHONDRIUM (Due to CML/CLL)

P/C

Worsening of heaviness in Left Hypochondrium →2-3 months

Patient presented with a complaint of dragging sensation/ worsening of heaviness (or mass) in the left upper abdomen that is gradual in onset, progressive in nature and 2-3 months in duration. According to the patient, he first noticed mild sensation of heaviness almost 6-7 years back (mass→ small in size that of a lemon) but he never visited a doctor .It progressed over period of years and now for the last 2-3 months. it has reached upto the umbilicus . The mass does not become prominent on neck flexion or any other movement of the body and neither reverted on compression (rule out extra- abdominal mass). It has no any aggravating or reliving factors. It is associated with ↓ appetite, early satiety, paleness of complexion, easy brusibility & recurrent nose bleeding and sometime fever at night. However, there is no HX of .....

DDs

- **Haematological malignancy** (lymphoproliferative and myleoproliferative disorder) → See Care
- **Lymphomas** →there is no Hx of lumps and bumps
- **Hemolytic anemia** →no HX of recurrent jaundice associated with paleness of complexion
- **Thalassemia major** →there is no HX of recurrent blood transfusion
- **Infective aetiology**
  - **Infective endocarditis** →there is no HX of valvular heart disease and HX of IV drug abuse
  - **Chronic malaria (tropical splenomegaly)**→ there is no HX of recurrent mosquito bite
  - **Infectious mo[illegible]osis** →there is no HX of recent sore throat
  - **Brucellosis** → there is no HX of contact with animals or ingestion of unpasteurized milk
  - **Enteric fever** → no HX of stepladder fever ,abdominal pain and diarrhea
  - **Disseminated TB and HIV** →no HX of contact with TB patient and high risk sexual behaviour
  - **Leishmaniasis (Kala azar)**→ no HX of fly/tick bite and pigmented skin lesion at site of bite
- **CLD and or portal vein thrombosis** →there is no HX of blood in the vomiting , black color stool
- **Autoimmune disorder RA (felty syndrome) SLE** →no HX of joint pain , skin rash and morning stiffness
- **Amyloidosis and sarcoidosis**

CARE /RECA

Risk and aetiology are same as discussed in lymphoma are same.

Complications (and association)

- **PRV**(only in in suspected case of CML) → HX of plethoric face , itching after hot bath and early onset HTN
- **Essential thrombocytosis**(only in suspected case of CML) → blurring of vision , Hyperviscosity of blood and HX of use of blood thinning medication

Scanned with CamScanner

- **Mets** (Head to toe)→ ask brief relevant complications of whole body
- **Recurrent infection**
- **Pigmented gall stones**

Now ask relevant

ITP and

PAM-HUGS-FOSS-TV-F

Examination

Same as discussed for lumps and bumps

VIVA Chronic Myeloid Leukemia

How will you investigate this patient?

- **CBC**→ with variable raised TLC (neutrophils) often > 100×10^9/L and normocytic normochromic anemia
- **Peripheral Smear** →demonstrates myeloid series shifted to left with dominant mature cells esp neutrophils and myelocytes and blast cell constitute less than 5-10% (However , in the blast phase→ Blast cells are >20%). there is also raised basophil , eosinophil and nucleated red cells .
- **Cytogenetic analysis of the patient's bone marrow and peripheral blood** →to detect BCR-ABL translocation) t(9:222, 95% sensitivity) by PCR ,chromosomal analysis(karyotyping) to detect Philadelphia chromosome and morphologic evaluation to confirm the stage of CML
- **Leukocyte alkaline Phosphate** → ↓
- **LDH, B12 and uric acid** → raised

What are the (WHO) phases of CML?

- Chronic phase → < 10% blast in the peripheral blood and bone marrow
- Accelerated Phase → 10-19%....
- Blast Phase → ≥ 20% ...

How will you treat this patient?

In chronic-phase of CML, the goal of treatment is to normalize the hematologic abnormalities and suppression of uncontrolled proliferation of malignant cells. The treatment of choice is five available tyrosine kinase inhibitor for 18 months-2 years (1st line imatinib, nilotinib, dasatinib while 2nd line are Ponatinib and Bosutinib) that targeting the aberrantly active abl kinase. Imatinib (400 mg/day) was the first tyrosine kinase inhibitor and it results in nearly universal (98%) hematologic control of chronic-phase disease. The rate of a major molecular response with imatinib in chronic-phase disease is -30% at 1 year. The second-generation tyrosine kinase inhibitors, nilotinib and dasatinib, are also used as front-line therapy and have higher the rate of a major molecular response (71% for nilotinib at 300-400 mg twice daily by 2 years, 64% for dasatinib at 100 mg/day by 2 years) compared to imatinib and also result in a lower rate of

Scanned with CamScanner

progression . A dual ber/abl tyrosine kinase inhibitor, **Bosutinib**, is used for refractory or intolerant cases. Common adverse effects of all tyrosine kinase inhibitors are QT-prolongation, skin rash and cytopenias.

Patients taking tyrosine kinase inhibitors should be monitored with a quantitative PCR assay. Those with a consistent increase in ber/abl transcript or those with a suboptimal molecular response should undergo all mutation testing and then switched to an alternative tyrosine kinase inhibitor. Specifically, The T315f mutation is resistant to all except third-generation agent Ponatinib (higher rate of vascular thrombosis). Patients who are resistant to tyrosine kinase inhibitors, including Ponatinib, the allosteric inhibitor asciminib can be added to therapy **(Recent Advances)**. It has shown a 54% complete haematological response and 48% sustained major response in heavily pre-treated patients, it major adverse effect are asymptomatic lipase elevation level and full blown pancreatitis

Omacetasine (a non-tyrosine kinase inhibitor) is used for CML patients who are resistant to at least two tyrosine kinase inhibitors. Patients in whom a good molecular response to any of above-mentioned agents cannot be achieved or in whom disease progresses despite therapy should be consider for allogeneic stem cell transplantation

Treatments of **Accelerated and blast crisis** are more challenging. For patients in accelerated phase, Tyrosine kinase inhibitor therapy is indicated (most commonly higher doses of nilotinib or dasatinib) .When blast transformation occurs the type of blast cell should be determined, as response to acute lymphoblastic leukemia is better than myeloblatic leukemia (80% transformation). For Accelerated and blast crisis causing extreme hyperleukocytosis (Priapism, altered mental status and visual blurring) urgent leukapheresis with immunosuppressive is indicated. Since the duration of response to tyrosine kinase inhibitors in this setting is limited, patients (younger and fit) who have accelerated or blast phase disease should ultimately be considered for allogeneic stem cell transplantation .Hydroxycarbamide can be an effective single agent and low -dose cytarabine can also be used palliative in older patients

How will you check /monitor CML response to treatment?

We can assess response to treatment by three different way eg haematological, cytogenetic and molecular responses

- **Haematological Complete Remission** →characterized by normal blood counts and splenomegaly within 3 month of treatment
- **Cytogenetic response** → reduction of BCR/ABL transcript to less than 10%(or ≥35%) within 3-6 months
- **Major molecular response** → reduction of Philadelphia chromosome (quantitative analysis) >3 log (or became ≤0.1 transcript) in 1 year

Prognosis (kindly check it on your own as below mentioned prognosis were recorded during a lecture)

- With treatment 10-year survival is 100%

Scanned with CamScanner

- Without treatment 3-4 year survival
- Blast crisis without treatment 6 months survival
- Cause of death →Blast crisis and infection

Chronic Lymphocytic Leukaemia (CLL)

Median age of presentation is 65-70 years

How will you investigate this patient?

- **CBC** → raised TLC (lymphocytosis)
- **Peripheral smear** → Mature lymphocytes and Smudge cell
- **Direct coombs test** →autoimmune hemolytic anemia
- **Serum immunoglobulin level (by electrophoresis)** → to ascertain the degree of hypogammaglobulinemia
- **Immuno-phenotyping** →Peripheral blood flow cytometry to confirm the diagnosis of CLL .this test ll shows the cell to be B-cells characteristically positive for CD5,CD19 and CD23
- **Bone marrow examination** →routinely not done but may be helpful in difficult cases for diagnostic evaluation of unclear cytopenias, or FISH or molecular genetics in case where peripheral blood cell lymphocytosis does not allow adequate immunophenotyping .Additionally ,it is also helpful to monitor response to therapy

What are the poor prognostic factors?

The main prognostic factor is the stage of the disease. Poor prognostic factors are as below

- Male gender
- Age >70-year
- Lymphocyte doubling time < 12 months
- CD38 expression positive
- Lymphocyte count > 50
- Prolymphocyte comprising > 10% of blood lymphocyte
- Deletion of part of the short arm of chromosome 17 (del 17p)

What are the indications of treatment in CLL?

- No specific treatment is indicated during very early stage (stage A) .However , the following are indications for treatment
- Evidence of bone marrow failure →development or worsening of anemia or thrombocytopenia
- Massive(>6cm) or progressive splenomegaly
- Massive(>10cm) or progressive lymphadenopathy
- Lymphocyte doubling time < 12 months or
- Progressive lymphocytosis→ >50% increase over 2 months or lymphocyte doubling time < 6 months
- Auto immune hemolytic anemia or thrombocytopenia(2 ITP)

Scanned with CamScanner

- Systemic symptoms like weight loss > 10% in 6 month , fever >38% for >2 weeks , night sweats and extreme fatigue

What are the staging systems of CLL

Staging of chronic lymphocytic leukemia

Binet staging of CLL
Stage A (60% patients)
• No anaemia or thrombocytopenia • and less than three areas of lymphoid node involvement
Stage B (30% patients)
• No anaemia or thrombocytopenia , • three or more involved areas of lymphoid node involvement
Stage c (10% patients)
• Anaemia and / or thrombocytopenia , • regardless of the number of areas of lymphoid node involvement

LN involvement or enlargement includes cervical, axillary, inguinal and liver and spleen.
There is another staging score called **Rai staging**→ Rai stage II and onward are indication for treatment

Rai staging

- **Stage 0:** Lymphocytosis, no lymphadenopathy, no hepatosplenomegaly, no anaemia or no thrombocytopenia
- **Stage 1**: Lymphocytosis with lymphadenopathy, no hepatosplenomegaly, no anaemia or no thrombocytopenia
- **Stage II:** Lymphocytosis with hepatomegaly or splenomegaly, with or without lymphadenopathy.
- **Stage III**: Lymphocytosis with anaemia with or without hepatomegaly or splenomegaly or lymphadenopathy.
- **Stage IV:** Lymphocytosis with thrombocytopenia with or without lymphadenopathy, hepatomegaly, splenomegaly or anaemia.

Risk group:

- Low risk: Rai stage 0.
- Intermediate risk: Rai stages II and I.
- High risk: Rai stages III and IV.

Scanned with CamScanner

Treatment of CLL

Patients who are aged less than 70-year fit (and TP53 mutation negative) **FCR** (Fludarabine, Cyclophosphamide and Rituximab) is the first line treatment while for older and less fit individual obinutuzumab is combined with bendamustine and oral chlorambucil. However if there is hemolytic anemia fludarabine should be avoided as this may exacerbate hemolysis and prophylactic measures like Co-trimoxazole should be taken before chemo with this agent as this also predispose to Pneumocystis Jiroveci pneumonia . If CLL is refractory to the above-mentioned therapy then we have option like ibrutinib (oral agent 420 mg /day, a Bruton tyrosine kinase inhibitor targeting B-cell receptor signalling) or venetoclax (400mg/day, a BCL2 inhibitor resulting in apoptosis) in combination with obinutuzumab (anti-CD20 antibody) therapy. Ibrutinib is associated with hypertension, cardiac arrhythmias, and rash and increased infections while Venetoclax is associated with tumor lysis syndrome and neutropenia.

For patients with relapsed or refractory disease, besides venetoclax, ibrutinib and or another BTK inhibitor, acalabrutinib, that has shown significant activity, other options includes idelalisib (150 mg orally BD) and duvelisib (is 25 mg orally BD) (inhibitors of P13 kinase delta).There are risks for colitis, drug-induced liver injury, and serious infectious complications.

Autoimmune hemolytic anemia or immune thrombocytopenia may be treated with rituximab, prednisone, or splenectomy. Patients with recurrent bacterial infections and hypogammaglobulinemia may be treated with prophylactic infusions of gamma globulin (0.4 g/kg/month).

Allogeneic transplantation is curative treatment for patients with CLL, but it should be used as final option only in patients whose disease cannot be controlled by the current available therapy

Complications of CLL

- recurrent infection due to hypogammaglobulinemia
- autoimmune complication like hemolytic anemia(10-15%) and immune thrombocytopenia
- Richter's transformation →transformation of CLL to high grade lymphoma

Differential diagnosis of CLL

- **mantle cell lymphoma (MCL)**
- These tumour cells express B-cell surface antigens and also express CD5, but usually not CD23.
- For cases that express CD23, staining for cyclin D1 or SOX11 and fluorescence in situ hybridisation (FISH) for detecting a translocation (11;14) are useful for establishing the diagnosis of MCL.
- **small lymphocytic lymphoma (SLL)**
- In the WHO classification, small lymphocytic lymphoma (SLL) and CLL are considered to be a single entity. CLL is effectively the same disease as SLL except the disease is found mostly in the bone marrow or blood While SLL is found mostly in lymph nodes The diagnosis of SLL requires the presence of lymphadenopathy and/or-splenomegaly with a number of B-lymphocytes in the peripheral blood not exceeding 5 x 10^9/l.

Scanned with CamScanner

- SLL cells show the same immunophenotyping as CLL
- The diagnosis of SLL should be confirmed by histopathological evaluation of a lymph node biopsy, whenever possible.
- **monoclonal B-lymphocytosis' (MBL)** .
- In absence of lymphadenopathy, organomegaly, cytopenias and clinical symptoms, the presence of fewer than 5000 monoclonal B lymphocytes/µl defines monoclonal B-lymphocytosis' (MBL).It can be detected in 5% of subjects with normal blood count. Progression to CLL occurs in 1%-2% of MBL cases per year.

Prognosis

Patients with stage 0 or stage I disease have a median survival of 10-15 years. patients may be reassured that they can live a normal life. A patient with stage III or stage IV disease with current therapies, 5-year survival is more than 70%. For patients with high-risk and resistant forms of CLL, allogeneic transplantation can lead to long-term disease control.

Hairy cell Leukemia

Salient features

- It is a rare chronic B-cell lymphoproliferative that characteristically express CD25 and CD103
- Middle-aged men ≥ 55 years
- Symptoms due to massive splenomegaly
- No lymphadenopathy

How will you investigate this patient?

- **CBC** → pancytopenia
- **Peripheral smear** →cells with numerous cytoplasmic projections called **hairy cells**
- **Bone marrow biopsy** → dry tap(inadequate material) hairy cells that characteristically stain with tartrate-resistant acid phosphatase (TRAP)

How will you treat this patient?

- Treatment of choice is nucleoside analogue pentostatin and cladribine (CD regimen) .this result in complete remission in 70-95% cases in a single course.
- Relapse cases should be retreated with the same agents
- Rituximab alone or in combination with the above-mentioned agents should be used in relapse/refractory disease .Additionally, Vemurafenib (BRAF inhibitor) and moxetumomab pasudotox (recombinant CD-22 targeting immunotoxin) is also indicated in relapse/refractory cases.

Scanned with CamScanner

ACUTE MYELOID LEUKAEMIA (AML)

Acute Myeloid Leukaemia is the most common form of acute leukaemia in adult and may occours as a primary disease or following a secondary transformation of a myleoproliferative disorder. Chemotherapy containing alkylating agents increases the risk of AML. Acute leukemia is defined by presence of > 20% of immature blasts in the bone marrow .It presents with vague and non-specific symptoms with mild splenomegaly, blurring of vision and drowsiness due to leucostatsis and Hyperviscosity due to high leukocyte count.

Risk factors in acute myeloid leukemia	
Good prognostic factors	**Poor prognostic factors**
• De novo disease • Favourable cytogenetic: t(15; 17) t(8; 21) or inv(16) or its variant t(16; 16) • CEBPA bi-allelic mutation • NPM1 mutation with FLT3 wild type	• Age >60 • Male gender • Secondary disease, e.g. prior MDS or MPN • High WBC • Adverse cytogenetics: -5, del(5q),-7, abnormal 3q26 or a complex karyotype • FLT3 internal tandem duplication mutation • MRD positivity

How you will investigate this patient?

- **CBC** → pancytopenia
- **Peripheral smear** → However, blasts may be absent from the peripheral smear in as many as 10% of cases known as aleukemic leukemia. it may also demonstrates the Auer rod (an eosinophilic needle-like inclusion in the cytoplasm) is a characteristic of AML .this may also be seen in some APL, high-grade MDS, and Myeloproliferative disorders.
- **Bone marrow** is usually confirming the diagnosis showing hyper -cellular and containing blasts more than 20%.
- **Flow cytometry and immunochemistry** →AML cell express myeloid surface marker like CD13 ,CD33 and also myeloperoxidase
- **Uric acid** → may be raised
- **Coagulation profile (M3)**→ PT, APTT D- dimers , fibrinogen level and fibrinogen degradation product
- **LP for blast cell in CSF** →for CNS involvement that is common in monocytic AML(5%)
- AML cells stain positive for sudan black and myeloperoxidase but M4 and M5 cells stain for NSE (non-specific esterase) while M6 cells stain positive for PAS (Periodic acid-Schiff)

For planning therapy

- RFTs ,LFTs 2D ECHO
- HLA type and
- HBV status

Scanned with CamScanner

What are the good prognostic and poor prognostic factors in AML?

Good prognostic factor

- Promylelocytic leukemia t(15;17)
- t(8;21)
- Inv 16 or t(16;16)

Poor prognostic factors

- Age >60 year
- > 20% blast after first cycle of chemo
- Bone marrow cytogenetic →deletion of chromosome 5 or 7

What is FAB (French –American-British) classification of acute myeloid leukemia?

- **MO** - undifferentiated
- **M1** - without maturation
- **M2** – with granulocytic maturation
- The most common (25% of adult AML).Associated with a t (8;21) translocation.
- **M3** - acute promyelocytic (APL)
- Has the best prognosis of all the subtypes of AML. Unlike other AML subtypes, APL is treated with all- trans retinoic acid (ATRA).t (15;17)
- **M4** – granulocytic and monocytic maturation
- Associated with a t (16;16) translocation
- **M5** – monocytic
- **M6** – erythroleukaemia
- **M7** – meg karyoblastic

How will you treat this patient?

Objective→ Acute leukemia is considered a curable disease, especially among younger patients without significant premorbid condition. The initial step is to obtain complete remission(CR), defined as normal peripheral blood with resolution of cytopenias, normal bone marrow with no excess blasts, and normal clinical status. Specific treatment depends upon the subtype of acute leukemia. Treatment can be broadly divided into supportive and specific treatment.

Supportive care

- **Correction of anemia** →transfusion of packed cell to keep HB > 8-10g/dl
- **Prevention and correction of bleeding** → transfuse platelets if $<10\times10^9$/L in the stable patients and $<20\times10^9$/L in the septic patient or $<50\times10^9$/L when the patient is undergoing a procedure like LP
- **Correction of coagulation profile** → transfuse FFPs to keep INR < 1.5 times normal and cryoprecipitate to keep fibrinogen level>1.5g/dL .Moreover, norethisterone is indicated to minimize menstrual loss in thrombocytopenic women
- **Leucopheresis**→ indicated before chemotherapy when there is Hyperviscosity symptoms
- **Control of Hyperuicaemia or tumor lysis syndrome** → with hydration and prophylactic allopurinol
- **Treatment of infection** →Prophylactic and therapeutic

Scanned with CamScanner

- **Psychological support**

Specific treatment (age < 60-year)

Induction of remission (CD regimen → cytarabine and daunorubicin).

Patients with AML who are treated with combination of an anthracycline (daunorubicin or idarubicin) plus cytarabine (anti-metabolite inhibit DNA synthesis, either alone or in combination with other agents (eg. Gemtuzumab a antiCD33 antibody). This therapy will produce complete remissions in 80-90% of patients under age 60 years and in 50-60% of older patients. Patients with secondary AML (AML evolved from prior Myelodysplastic or Myeloproliferative disorders) or treatment-associated AML should receive the daunorubicin and cytarabine).

Maintenance of the remission

Once remission is achieved, treatment option includes further chemotherapy and allogeneic cell transplantation. Patients with a favourable genetic (inv (16) or t (8; 21) etc) can be treated with chemotherapy alone or with autologous transplant with cure rates of 60-80%. For intermediate risk (normal karyotype +8, +21) patients AML, cure rates are 35-40% with chemotherapy and 40-60% with allogeneic transplantation. Patients who do not achieve remission (primary induction failure) or those with high-risk genetics (-7, -5 complex karyotype) have cure rates of less than 10% with chemotherapy alone and therefore are referred for allogeneic stem cell transplantation

Specific treatment (age >60-year)

The treatment in this age group is more contentious and treatment related morbidity, and mortality is also more common.

These Patients can be treated with newer targeted agents, including the bcl2 inhibitor venetoclax added to a hypomethylating agent or low-dose cytarabine, enasidenib (targeting IDH2 mutations), ivosidenib (targeting IDH2 mutations), or glasdegib. Some of these patients can still benefit from a reduced-intensity allogeneic transplant if they achieve good disease control.

Relapsed AML

Treatment is based on indiduvals basis; however, overall prognosis is very poor. For patients in second remission, allogeneic transplantation offers a 20-30% chance of cure. Targeted therapies discussed above are useful for selected patients and may offer long-term disease control.

Acute promyelocytic leukaemia (APML)

Acute promyelocytic leukaemia (APML) is a variant (M3) of AML, with 10-15% of cases, it is characterized by the translocation t (15; 17).it is characterized by coagulopathy (DIC), which remains a major cause of death. All-trans-retinoic acid (ATRA) causes differentiation of promyelocytes and rapid reversal of the bleeding tendency. APML is treated with ATRA combined with several courses of chemotherapy (arsenic trioxide ± gemtuzumab (anti-CD33). Complete remission occurs in at least 90% of younger adults with APML, and at least 70% will expect to be cured. Transplantation may be necessary either if the leukaemia is not cured or following recurrence and re-induction therapy. Arsenic trioxide, (induces apoptosis) is used in resistant or relapsed disease and may be possibly used as first-line therapy in future.

Scanned with CamScanner

ACUTE LYMPHOBLASTIC LEUKAEMIA (ALL)

ALL is a disease of children with peak incidence 2-5 years and 2nd peak in old age. However, in adult prognosis is unfavourable

Classification (WHO)

- B-cell ALL →almost 80-85%
- T-cell ALL→ 15-20%

Risk factors

Children with following conditions are at risk for ALL

- Down syndrome
- NF1
- Bloom syndrome
- Ataxia telangiectasia

How will you investigate this patient?

(Specific only)

- **Chest-x-ray**→ mediastinal mass
- **LP**→ blast in CSF (5%) in meningeal **leukaemia**
- **Flow cytometry and immunohistochemistry**→ ALL of B-cell lineage shows CD19 and CD10 while ALL of T-cell lineage CD2,CD5 and CD7
- **Peripheral smear** → shows lymphoblast cells and TdT (95%)
- **Bone marrow** → > 25% lymphoblast in the bone marrow and is diagnostic test
- **FISH Study** → for Philadelphia chromosome (poor prognostic factor in ALL)
- **Testicular ultrasound** → scrotal involvement although rare

ALL is characteristically stain positive for PAS (periodic acid-Schiff) and NSE (non-specific Esterase)

How will you treat this patient?

ALL may present in leukemic phase with marrow infiltration (acute lymphoblastic leukaemia) or may present as localized disease typically present with a mediastinal mass (lymphoblastic lymphoma) .However, treatment is same for both aforementioned types.

Treatment is VDAP regimen

Adult patients with ALL are treated with combination chemotherapy called VDAP regimen (vincristine, daunorubicin, asparginase and prednisone). This result in complete remissions in 90% of patients. Those patients with Philadelphia chromosome-positive ALL (bcl-abl positive ALL) should receive a tyrosine kinase inhibitor, such as dasatinib or Ponatinib, added to VDAP regime .in ALL Patients should also receive CNS prophylaxis so that meningeal sequestration of leukemic cells does not develop contrary to AML .

Once complete remission is achieved, either patients may be treated with additional cycles of chemotherapy alone or high-dose chemotherapy and stem cell transplantation based on patient age and disease risk factors. Patients younger than 39 years have uniformly better outcomes when

Scanned with CamScanner

treated under paediatric protocols. For older high-risk patients will not be cured with chemotherapy alone and therefore they will need allogeneic transplantation

. For patients with relapsed disease, blinatumomab (anti CD19) and the antibody-drug conjugate inotuzumab ozogamicin (anti CD22) are considered superior to traditional chemotherapy. Tisagenlecleucel is a therapy utilizing autologous T cells engineered to express an anti-CD-19 antigen receptor (CART-19) indicated for treatment of children and younger with relapsed and or/refractory B-ALL

Prognosis

Prognosis of ALL in childhood is excellent with complete remission in almost all patients with 80% being alive without recurrence at 5 years .While the prognosis is not favourable for adult and getting worse with advancing age. Patients with adverse cytogenetics, poor response to chemotherapy, or older age have a much lower chance of cure (cure rates of 20-40%).

ALL risk factors

Risk factors	Good prognostic factors	Poor prognostic factors
Age→	Younger	Older
WBC→	<50×10^9/L for B-lineage B-lineage	>50×10^9/L for B-lineage
	<100×10^9/L for T-lineage	>100×10^9 T-lineage
Immunophenotyping→	CD10+ common ALL	B or T cell surface markers
Cytogenetic translocation→	t(12; 21) hyperdiploidy	t(9; 22) or t(4; 11) hypodiploidy
Time to response→	Early clearance of blasts	Failure to achieve complete remission within 3-4 weeks
Minimal residual disease(MDR)→	MRD negative	MRD positive
Extra medullary disease→	CSF clear	CSF positive
Others→	Del(9p) FAB L1 type Pre-B phenotype	Male gender CNS involvement FAB L3 type

Scanned with CamScanner

Different between ALL and AML

Features	ALL	AML
Presence of Auer rods in blood	None	Always present
Presence of lymphoblast on blood	Always present	May or may not be present
Bone and joint pain	More common	Less common
Hepatosplenomegaly	More common	Less common
Organ infiltration	More common	Less common

Essential Thrombocytosis / Thrombocythaemia

It is myeloproliferative disorder characterized by marked proliferation of the megakaryocytes in the bone marrow result in raised level of platelets.

Features

- Most commonly present at the age of 50-60 years
- Thrombosis at unusual site like mesenteric ,hepatic and or portal veins
- Erythromelagia eg redness and painful burning of hands relived by aspirin
- Mucosal bleeding due to qualitative defect
- Splenomegaly (25%)

How will you investigate this patient?

- **CBC**→ raised platelet (2000 x 10/L); WBC count is also mildly raised while The hematocrit is normal.
- **The peripheral smear** →reveals large platelets, and with some immature myeloid cells
- **Bone marrow biopsy** →shows increased numbers of megakaryocytes
- **JAK-2, CALR and MPL mutation** → positive mutation support the diagnosis but it is not universal
- **FISH study** → to check for Philadelphia chromosome (bcr/abl) to exclude CML

How will you treat this patient?

Patients are divided into high risk and low risk of thrombosis and are managed differently

High-risk patients

These include patient's age > 60 years; have a leukocyte count of ≥ 11,000/mcl (11 x 10^9/L) or have a previous history of thrombosis. Interestingly, they are also at high risk for bleeding.

Scanned with CamScanner

The risk of thrombosis is reduced by keeping platelets counts below 500,000/mcl. (500×10^9/L) with following drugs. .The treatment of choice is oral hydroxyurea (500-1000mg/day). In cases where hydroxyurea is not well tolerated because of anemia, low doses of anagrelide (, 1-2 mg/day orally. MOA→ inhibitor of megakaryocyte maturation), may be added. As Higher doses causes headache, peripheral edema, and heart failure. Pegylated interferon alfa-2 potentially targets the malignant clone in CALR-mutant cases. While intravenous radioactive phosphorus (^{32}P) may be a useful therapy in old age .Additionally, coexistent cardiovascular risk factors must be addressed in all patients.

Low risk patients

(Age <40 years, platelets counts $<1500\times10^9$, no HX of thrombosis and bleeding)

Low-dose aspirin (81 mg/day orally) has been used to reduce the risk thrombotic complications in the group of patient. Recently it is recommended that twice-daily aspirin is more beneficial than OD dose. A vasomotor symptom such as erythromelagia and paresthesia also respond to aspirin .Plateletpheresis is indicated for severe bleeding.

Differential Diagnosis

In cases of marked thrombocytosis ≥1,000,000/mcL [1000×10^9/L)) or any evidence of bleeding, acquired von Willebrand syndrome must be excluded before starting low-dose aspirin

Complications

There is a 10-15% risk of progression to mylofibrosis after 15 years, and a 1-5% risk of transformation to acute leukemia over 20 years. Late in the disease course, the bone marrow may become fibrotic, and massive splenomegaly may occur that is may be complicated by splenic infarction

Polycythaemia Rubra Vera

It is myeloproliferative disorder characterized by overproduction of all 3 cells-lines predominantly red blood cells .It occours in patients over age of 40 and may presents with either plethoric face due to raised HB or headache, blackout, pruritus after hot bath epistaxis and lassitude due to hyperviscosity .Additionally, patients may have peptic ulcer disease, venous thromboembolism, peripheral arterial and cerebrovascular disease and bleeding. Patients have splenomegaly

How will you investigate this patient?

- **CBC**→ Hematocrit > 49% in males or > 48% in females. The white blood counts are elevated to 10,000-20,000/mcL and Platelet count is also raised that may exceed 1,000,000/mcl ($1000x10^9$/L). Additionally, there is basophilia and eosinophilia
- **ESR**→ low
- **JAK2 mutation** →screening test and positive mutation confirm the diagnosis
- **Erythropoietin level** → suppressed /Low
- **Vit B12 level** →strikingly raised due to secretion of transcobalamine III by white blood cells
- **Uric acid level** → raised
- **Serum ferritin** – may be low
- **Leucocyte alkaline phosphatase (LAP)**→ raised
- **Bone marrow**→ pan hyperplasia of all three cells –line but it is not done routinely

Scanned with CamScanner

- **Investigation to exclude secondary causes**
  - Red cell mass (normal)
  - Arterial oxygen saturation
  - Abdominal ultrasound
  - Serum erythropoietin
  - Cytogenetic analysis
  - Bone marrow aspirate and trephine
  - Erythriod burst-forming unit (BFU-E) culture

What is the revised WHO criterion of polycythaemia?

Diagnosis requires the presence of both major criteria and one minor criterion, or the presence of the first major criterion together with two minor criteria.

Major criteria

- Red Haemoglobin >185 g/L in men, > 165 g /L in women or other evidence of increased red cell volume
- Presence of JAK2 tyrosine kinase V617F or other functionally similar mutation such as JAK2 exon 12 mutation

Minor criteria

- Bone marrow biopsy, showing hypercellularity for age with trilineage growth with prominent erythriod, granulocytic and megakaryocytic proliferation
- Serum erythropoietin level below the reference range for normal
- Endogenous erythroid colony (EEC) formation in vitro.

What are the Causes of polycythaemia?

Primary

- Polycythaemias Rubra vera

Congenital

- Mutations in erythropoietin receptor

Scanned with CamScanner

Secondary causes (A) Due to hypoxia induced erythropoietin • High altitude • Chronic lung conditions • Cardiovascular diseases (right to left shunt) • Sleep apnoea • Morbid obesity • Heavy smoking Relative • Stress induced polycythaemia • Dehydration and burns High –oxygen-affinity haemoglobin •	(B)Due to pathological increase in erythropoietin • Renal diseases like renal cell carcinoma and wilms tumour • HCC • Cerebellar heamangiobalstoma • Massive uterine leiomyoma • Over, administration of erythropoietin and estrogen

How will you treat this patient?

Venesection Initially, the treatment of choice is phlebotomy. One unit of blood (400-500 mL) is removed weekly until the hematocrit is less than 45%; the hematocrit is maintained < 45% by repeated venesection as necessary. As iron deficiency develops with repeated phlebotomy the frequency of phlebotomy should gradually be reduced with aim of maintaining a PCV of <O.45L/L.

Chemotherapy

Patients who cannot tolerate phlebotomy or have uncontrolled disease (like thrombosis, symptomatic splenomegaly, intractable pruritus and thrombocytosis) may be best managed with hydroxyurea (500-1500mg/day. The dose is adjusted to, to keep platelets less than 500,000/mcL (500x 10^9/L) without reducing the neutrophil count to less than 2000/mcL (2.0 x 10^9/L).

The JAK2 inhibitor ruxolitinib (10mg BD max dose is 25mg BD) is FDA-approved for patients resistant or intolerant to hydroxyurea.

Alkylating agents, such as busulfan may be more convenient for elderly, but associated with increase the risk of conversion to acute leukemia and therefore should be avoided. Anagrelide is indicated for uncontrolled thrombocytosis.

Low-dose aspirin has been shown to reduce the risk of thrombosis without excessive bleeding and should be given to all patients without contraindications to aspirin.

Supportive care

- Allopurinol 300 mg orally daily may be indicated for hyperuricemia.

Scanned with CamScanner

- Antihistamine therapy with diphenhydramine or other H_1-blockers are commonly used to manage pruritus.

Recent Advances

- ropeginter- feron alfa-2b has been recently approved by the European Medicines Agency as first- -line therapy for patients without symptomatic splenomegaly
- A new therapeutic strategy is induction of apoptosis via the p53 pathway through inhibition of human double minute 2 (mdm2) is under trial.

Prognosis

The major cause of morbidity and mortality is arterial thrombosis. Over time, polycythaemia Vera may convert to mylofibrosis or CML. In 5% of cases, the disorder progresses to AML, which is mostly refractory to standard therapy.

Scanned with CamScanner

Myelodysplastic Syndromes (MDS)

Myelodysplastic Syndromes also called myelodysplasia is a group of acquired bone marrow (Haematopoietic stem cells) disorder characterized by common features of ineffective blood cells production .The bone marrow is hyper cellular with dysplastic changes in one or more cell lines while the blood film is characterized by dysplastic cells ,blast cells (less than 20%) and cytopenias . It is the disease of old age and they are consider a pre-leukemic and may represent genetic steps in the development of leukaemia as transformation into acute myeloblatic leukemia occours in approximately 30% of cases .MDS may present in the elderly patients with with symptoms of anemia, recurrent infection or bleeding tendency due to pancytopenia

Risk factors

- Mostly idiopathic
- Prior exposure to chemo , radiation or both
- Genetic mutation of chromosome particularly 5 and 7

How will you investigate this patient?

- **CBC**→ marked anemia with the normal or increased MCV, WBC & platelets may be normal or reduced with neutropenia
- **Blood Smear** → macro-ovalocytes, myeloid series may be left shifted, and small number of promyelocytes or blasts may be seen. Additionally, the neutrophils may be deficient numbers of granules or deficient segmentation of the nucleus, even a bilobed nucleus (Pelger-Huët abnormality).
- **Bone marrow finding**→ characteristically hypercelluar bone marrow (and very rarely may be hypo). Ring sideroblasts (Prussian blue stain) myeloid series shifted to lift with variable number of blast. Dwarf megakaryocyte with a unilobed nucleus is the characteristic finding.
- **What is the WHO classification of MDS?**

WHO classification of MDS	
Name of the disease	Bone marrow features
Refractory anemia	< 5% blast cells
MDS with single-lineage Dyplasia	<5% blast cells
MDS with ring Sideroblasts (MDS-RS)	>15% ring sideroblasts or 6-14% and presence of SF3B1 gene mutation
MDS with multilineage dysplasia	<5% blast and dysplasia in≥ 2 lineages
MDS with excess blasts	5-19% blasts
MDS with isolated del(5q)	Myelodysplastic syndrome associated with a del (5q)cytogenetic abnormality <5% blasts Often normal or increased blood and platelet count
unclassifiable MDS	None of the above features

Scanned with CamScanner

Differentials

- Aplastic anemia
- Megaloblastic anemia
- Mylofibrosis
- HIV induced cytopenias

How will you treat this patient?

As MDS is the disease of old age, majority of the cases are managed conservatively with supportive care .Allogeneic stem cell transplantation is the only curative treatment but it is limited by the old age of the patient

- **Erythropoietin** → for patients with anemia and low serum erythropoietin level (≤500 units/L), erythropoietin may raise the hematocrit and reduce the red cell transfusion requirement
- **(G-CSF)** granulocyte colony-stimulating factor, Patients with severe neutropenia may benefit from filgrastin. Oral thrombopoietin analogs, like romiplostim and eltrombopag, is effective in raising the platelet count in myelodysplasia
- **Iron Chelation therapy** it is indicated in-patient who develop secondary iron due to multiple transfusion or having serum ferritin > 1000ug /L. the agent of choice is oral deferasirox (20 mg/kg/day in divided doses
- **Immunosuppressive therapy** like cyclosporine and antithymocyte globulin (ATG) in selected patients like age less than 60 years, absence of 5q- and presence of HLA DR15
- **Lenalidomide** (10 mg/day orally) is the treatment of choice in patients with MDS with isolated del(5q) with excellent responses in 70% of patients, that lasts > 2 years. It adverse effects are neutropenia and thrombocytopenia, but venous thrombosis sometime may also occur and that is why prophylaxis with aspirin is recommended. **Recently** luspatercept (target signaling via the SMAD2-SMAD3 pathway, which is c increased in patients with MDS) has been approved .It common adverse effects are diarrhea, lassitude, fatigue, nausea, and dizziness.
- **High-risk MDS patients'** hypomethylating agent like Azacitidine (dose of 75 mg/m² daily for 5-7 days every 28 days) is the treatment of choice that not only improves symptoms and blood counts but also prolongs overall survival and time to conversion to acute leukemia. Up to six cycles of therapy may be required to achieve a response. Decitabine, (20 mg/m² daily for 5 days every 28 days) has same hematologic responses but does not improve survival.

Prognostic Scoring system (Google it for detail information)

International prognostic scoring system (IPSS) based on parameters like % of bone marrow blasts, cytogenetics (Karyotype) and severity of cytopenias. Based on this score patient are divided into five groups for survival and transformation into acute leukemia.

Favourable prognostic factors

- Isolated del(5)
- Low blast cells
- Absence of adverse cytogenetics

Scanned with CamScanner

Unfavourable prognostic factors

- Excess blast cells
- Presence of Chronic myelomonocytic leukemia(CMML)

Prognosis

MDS is ultimately fatal disease and most common cause of death is infections or bleeding. Median survival for low risk patients is 6 years while only 5 months for high-risk patient

Primary Myelofibrosis

Primary Myelofibrosis is a chronic myleoproliferative disorder that is either a primary or develop lately as complication of essential thrombocytosis or Polycythaemia .there is clonal proliferation of stems cells and abnormal myeloid linage cells in the marrow, spleen, liver and other organs called extra medullary haematopoiesis due to bone marrow fibrosis in advance stage . Like MDS it is also disease of advance age (>50-years) and patients with non-specific features like nights sweats, splenomegaly and lethargy and weakness. It is believed palettes –derived growth factors (FDGF) and other cytokine trigger that bone marrow fibrosis. On examination patient may have splenomegaly while hepatomegaly is present in 50% of the cases

How will you investigate this patient?

- **CBC** →anemia universal feature while other cell line may be raised or low
- **Peripheral Smear** →triad of tear drop cells , leukoerythroblastic blood and giant platelets
- **Philadelphia chromosome** → absent and this differentiate it from other myeloproliferative disorders
- **Bone marrow biopsy** → dry tap due to fibrosis but during the very early stage may be hypercelluar(silver stain shows raised reticulin fibres)
- JAK-2 mutation is present in half of the case while CLAR mutation are present in the remaining cases

DDs based on leukoerythroblastic blood picture

- Severe infection
- Bone marrow infiltration by any pathology
- Inflammation

DDs based on dry bone marrow tap

- Hairy cell leukemia
- Hodgkin lymphoma
- Metastatic carcinoma

How will you manage this patient?

Patient is categorized into various group based on the dynamic international prognostic scoring system (DIPSS-Plus →Google it). Treatments is mainly supportive and depend on the risk group

- **Anemia**→ RCC transfusions are given to anemic patient's .However, Anemia can also be controlled with androgens, prednisone, thalidomide or lenalidomide.

Scanned with CamScanner

- **Splenomegaly** → for mylofibrosis induced splenomegaly Hydroxyurea (500-1000 mg/day orally) is the drug of choice reducing spleen size by half in 40% of patients. Additionally both thalidomide and lenalidomide may also reduce splenomegaly and improve thrombocytopenia in some patients. Indications of splenectomy are medication-refractory splenomegaly, severe thrombocytopenia, and or an unacceptable transfusion requirement.
- **High-risk patients** the treatment of choice is allogeneic stem cell transplant .However, candidates where transplant is not done for whatever reasons, they may be treated with Ruxolitinib, (JAK2 inhibitors) or immunomodulatory agents (lenalidomide) for symptom control. Ruxolitinib results in reduction of spleen size and improvement of symptoms but does not induce complete clinical or cytogenetic remissions. It is noteworthy that ruxolitinib may exacerbate cytopenias ,More recently The newer selective JAK2 inhibitor fedratinib, FDA approved in 2019, result in reduction in spleen size and symptoms improvement in patients with advanced- stage myelofibrosis. However, it may cause fatal encephalopathy, including Wernicke encephalopathy; therefore, thiamine level should be maintain within normal range. Lenalidomide and pomalidomide also result in improve anemia and thrombocytopenia in some cases, without significant reduction in splenic size in high risk group

Miscellaneous → radiation may improve painful sites of extra medullary hemato poiesis pulmonary hypertension and severe bone pain

Scanned with CamScanner

Multiple Myeloma (MM)

Multiple Myeloma (MM) may present with Backache (Follow approach to lower backache) or Anemia (follow approach to anemia) as the most common presenting symptoms. Multiple Myeloma is malignant proliferation of plasma cell in the bone marrow and account for 1% of all malignant disease. The peak incidence is patients aged 60-70 years.

How will you investigate this patient?

- **CBC** → Anemia is nearly universal.
- **Peripheral Smear** → of rouleaux formation (due to paraprotein) and rarely plasma cell
- **ESR**→ very high
- **RFTs**→ may be deranged
- **Serum calcium** → normal or raised
- **Total protein** → may be normal or raised
- **Serum or urine protein electrophoresis (PEP) or immunonofixation electrophoresis (IFE)** → may show monoclonal spike visible in the gamma- or beta- globulin region of the PEP. The semi-quantification of the paraprotein on the PEP is called the M-protein spike while IFE demonstrates this to be a monoclonal immunoglobulin. The paraprotein is IgG (60%), IgA (20%), or light chain only (15%) while rest are rare cases of IgD, IgM, or biclonal gammopathy.
- **24 hours urine electrophoresis (PEP) and immunonofixation**→ for the assessment of light –chain (as Bence - Jones protein). Approximately 15% of patients will have no paraprotein in the serum on PEP because their myeloma cells produce only light chains and not intact immunoglobulin and the light chains pass through the glomerulus into the urine.
- **Bone marrow** → confirmatory test where plasma cells are ≥ 10% and on flow cytometry, the plasma cells will display marked deviation of the normal kappa-to-lambda light chain ratio.
- **Skeletal survey** → lytic bone lesions in the skull
- **MRI Spine** → may show compression /collapse
- **Serum B_2- microglobulin**→ For prognosis

What is the diagnostic criterion of multiple myeloma?

The diagnosis requires ≥ 10% plasma cells in the bone marrow or biopsy –proven plasmacytoma plus evidence of one or more multiple myeloma defining events: famously known as CRAB (Hypercalcemia, renal failure, anemia and lytic bone lesions) attributed to the plasma cell disorder, bone marrow clonal plasmacytosis ≥60, serum involved /uninvolved free light chain ratio > 100(provided involved free light chain is ≥ 100 mg/L) or > 1 focal lesion on MRI. (Reference →PubMed article)

Alternative criteria

This diagnostic criterion for multiple myeloma require one major and one minor criterion or three minor criteria in an individual who has clinical feature suggestive of multiple myeloma.

Major criteria

- Plasmacytoma (as demonstrated on evaluation of biopsy specimen)

Scanned with CamScanner

- 30% plasma cells in a bone marrow sample
- Elevated levels of M protein in the blood or urine

While monoclonal proteins:

- in the serum (usually IgG or IgA)
- in the urine (Bence Jones proteins) →there is negative dipstick for protein and positive in biochemistry because Bence jones proteins are not detected dipstick

Minor criteria

- 10% to 30% plasma cells in a bone marrow sample.
- Minor elevations in the level of M protein in the blood or urine.
- Osteolytic lesions (as demonstrated on imaging studies).
- Low levels of antibodies (not produced by the cancer cells) in the blood.

What are the causes of anemia in multiple myeloma?

- Bone marrow infiltration by plasma cells
- Chronic disease
- Renal failure
- Drugs used in treatment

What are causes of renal failure in multiple myeloma?

- Recurrent urinary tract infection
- NSAIDs
- Secondary amyloidosis
- Paraprotein deposition(most common)
- Hypercalcemia

What are poor prognostic factor?

- High B_2-microglobulin >5.5 mg/L
- Low albumin
- Low hemoglobin (anemia)
- High calcium at presentation
- Viscosity
- LDH
- Recurrent bacterial infections

What is the WHO classification of plasma cell malignancy?

• Monoclonal gammopathy of undetermined significance (this should be your2nd DDs of MM) • Plasma cell myeloma • Solitary plasmacytoma of bone • Extraosseous plasmacytoma • Monoclonal immunoglobulin deposition disease	• **Heavy chain disease** **—gamma (ɣ) heavy chain disease** **—mu( ) heavy chain disease** **—alpha () heavy chain disease**

Scanned with CamScanner

Management

How will you treat this patient?

Treatment is broadly divided into supportive care and specific treatment

Supportive care

- Anemia → should be corrected with transfusion and or erythropoietin or both
- Infection should be promptly treated with antibiotics
- Bone pain may be relived with localized radiotherapy ,chemo or high dose dexamethasone .NSAID should be avoided to due risk of AkI
- Vertebral collapse can be treated with vertebroplasty or or kyphoplasty
- Pathological fracture →the bisphosphonates (zoledronic acid) or the denosumab (RANKL-inhibitor) reduces pathologic fractures in patients with bone disease.
- Hypercalcemia and hyperuricemia should be treated aggressively with immobilization , adequate hydration and with the bisphosphonates
- Oliguric or anuric kidney disease (due to deposition of free light chain) should be treated aggressively with chemotherapy and considered for plasma exchange (to remove the paraprotein) may return kidney function in some cases

Specific treatment

- The initial treatment generally involves triple therapy: lenalidomide an (immunomodulatory agent), s bortezomib or carfilzomib (protease inhibitors) and moderate- high- dose steroid like dexamethasone. An immunomodulatory agent is replaced with cyclophosphamide in case of kidney injury. The major side effects of lenalidomide are neutropenia and thrombocytopenia, thromboembolism, peripheral neuropathy, and birth defects. While the major side effect of bortezomib is peripheral and autonomic neuropathy, (minimize when given subcutaneously rather than intravenously). Carfilzomib rarely causes neuropathy but causes reversible pulmonary hypertension or cardiac systolic dysfunction.
- A combination of daratumumab subcutaneous (an anti-CD38 monoclonal antibody) plus hyaluronidase-fihj is recently approved for multiple myeloma including for patients not eligible for autologous bone transplant and relapsed or refractory patients.
- **Relapse cases** ixazomib (oral proteasome inhibitor) is indicated for relapsed cases .Additionally, Pomalidomide, is used for salvage therapy after relapse. Other salvage drugs are daratumumab, elotuzumab (an anti- SLAMF7 monoclonal antibody) and belantamab mafodotin (an anti-BCMA antibody conjugated to a cytotoxic agent).
- After initial therapy, many patients under age 80 years are treated with autologous hematopoietic stem cell transplant after melphalan therapy. It prolongs duration of remission and overall survival. Lenalidomide or thalidomide prolongs remission and survival when given as post-transplant maintenance therapy

Scanned with CamScanner

What are the life threatening complication of myeloma

- **Renal impairment-** mostly due to hypercalcaemia .Patients may renal replacement therapy
- **Hypercalcaemia** should be treated by adequate hydration and use of bisphosphonates such as pamidronate
- **spinal cord compression** is treated with dexamethasone followed by radiotherpy
- **Hyperviscosity** due to high circulating level of paraprotein may be treated urgently by plasmapheresis

How will you stage multiple myeloma?

There are three stages

Stage 1

- Hb>10 g/dl
- Calcium nor elevated
- Low M component
- Up to one lytic bone lesion

Stage 2

Intermediate stage between stage 1 and stage 3

Stage 3

- Hb<8.5 g/dL
- Calcium> 3 mmol/L

What is international prognostic index based on serum albumin and β –microglobulin (β_2 M) for multiple myeloma?

Stage	Median survival (months)
Stage 1 β_2M<3.5mg /L and Serum albumin ≥35 g/L	62
Stage 2- not stage 1 or 3	44
Stage 3 – β_2M >5.5mg/L	29

What are the Red flag signs of low back pain

- History of malignancy, immunosuppression and or HIV
- Age >50 years
- Fever and night sweat
- Lack of response to analgesia
- Night pain
- Thoracic pain
- > 1 months duration
- Neurological symptoms like
    - Lower limb weakness
    - Paraesthesia and sensory loss
    - Urinary retention

Scanned with CamScanner

APPROACH TO VARIOUS PRESENTATIONS OF IDIOPATHIC THROMBOCYTOPENIC PURPURA (ITP)

ITP presents with bleeding in different ways .For example, it may present with

- Gums bleeding
- Skin brusibility
- Menorrhagia and or/ haematuria

Additionally, the approach to ITP also depend whether it is isolated ITP or present with pancytopenia and lumps &bumps. Therefore

- ITP with lumps & bumps ,follow lumps and bumps approach
- ITP with pancytopenia , follow pancytopenia approach
- Isolated ITP , follow the below scheme

Gums bleeding ... 20 days

HOPI (ODPARA-V)

Patients presented with gums bleeding that is sudden in onset, progressively increasing in nature and 20 days in duration .Initially, patient experienced gums bleeding during brushing the teeth and it was only minimal just staining the teeth only but for the last 10 days patient has multiple episodes of bleeding that is 10-15 ml in quantity, fresh bright red in colour, occurring with and without brushing and has no specific timing, that not only stain the teeth's but also lips and oozes from mouth .it has no exacerbating factors and relived temporarily with cold water .it is associated with skin brusibility etc.

(At the end of HOPI, always comments on the other cell lines (RBC and WBC) like no HX of paleness of complexion and recurrent infection)

Menorrhagia

P/C

Excessive menstrual bleed

Patients presents with excessive menstrual bleeding from this period and number of pads /day , duration of cycles , painful or painless .bright red in colours having clots . This is associated with skin brusibility and HX of bleeding from any particular other body sites

At the end of HOPI, always comments on the other cell lines (RBC and WBC) like no HX of paleness of complexion and recurrent infection)

Skin brusibility

Patient present with skin brusibility that is gradual in onset, progressive in nature and... duration. Initially, it was pink/purple in colour, non-itchy, non-painful, palpable and does not follow specific pattern. Initially, patient responded to tranexamic acid but now does not improve with same medicine and also has changed the colour to blue. It has no reliving factors but aggravating with minimal trauma and is associated with bleeding from that particular site.

(At the end of HOPI, always comments on the other cell lines (RBC and WBC) like no HX of paleness of complexion and recurrent infection)

DDs (of the above presentations)

Scanned with CamScanner

- **Viral infections** (Dengue & EBV) → Hx of high grade fever , flu like symptoms , body aches and retrorbital pain
- **Hyperviscosity (PRV,MM and MCGUS etc)**→ HX of blurring of vision , musical sounds in the ear and HX of weakness of any part of the body
- **CLD** → HX of blood in the vomitus , black tarry stool and abdominal distension
- **CKD** →HX of decreased urine output , sallow complexion and uremic breath
- **Bleeding disorder** → Family HX of bleeding disorders like prolong bleeding after circumcision
- **Drugs** → HX of blood thinning medications
- **HUS** → HX of recent dysentery
- **TTP** → HX of altered sensorium , headache and weakness of any part of the body
- **HELP syndrome** → HX of pregnancy/recent childbirth and jaundice
- **Mechanical valve** → HX of valve implantation
- **Wiskot-Aldrich syndrome** →HX of itchy skin rash (eczema) since birth
- **Post-blood transfusion** → HX of recent transfusion

Primary ITP → No splenomegaly
Secondary ITP → Splenomegaly

Causes of Secondary ITP

- **Infection** like HCV , HBV , HIV and EBV
- **Autoimmune** like SLE and APAS
- **Evans syndrome** (HX of recurrent yellow discoloration of sclera and bleeding from body orifices)
- **Thyroiditis**
- **Drugs** like steroids , aspirin ,clopidogrel , heparin ,velproic acid , chemotherapy and immunosuppressant
- **Malignancy**

RECA /CARE

Complications of ITP

Mentioned complications of bleeding like stroke(IC bleed) , angina due to anemia , hypovolemic shock due to excessive bleeding , anemia from recurrent bleeding , black stools , swollen painful joint (haemarthrosis) and ask about complication of drugs like steroids(Cushingiods features) and immunosuppressant .

Now ask relevant

ITP and PAM-HUGS-FOSS-TV-F

Examination scheme

Vitals

Scanned with CamScanner

GPE →anemia, jaundice (AIHA), purpura (site, shape blanching, palpable, color and check tenderness), lymph nodes, bony tenderness, oral cavity for gums bleeds

Abdomen → splenomegaly (2 ITP)

CVS → unremarkable

Chest and CNS→ unremarkable

Fundascopy→ hemorrhage

VIVA of ITP

Primary ITP is the diagnosis of exclusion

- **CBC** →isolated thrombocytopenia
- **Peripheral Smear** → may show occasional giant cell and exclude leukemia
- **Bone marrow**→ increased numbers of megakaryocytes

Bone marrow indications are

- ≥2 cells line affected
- isolated thrombocytopenia in patients > 40 years and
- when ITP patient doesn't respond to primary treatment

- **antiplatelet antibodies IIb-IIIa or glycoprotein Ib-V-IX complex** → investigation of choice but detection of such antibodies is not essential for diagnosis
- **CT and BT** → normal while BT raised in haemophilia
- **PT,aPTT** →normal
- **Investigations to exclude secondary cause of low platelets**
  - antiHCV and HbsAg
  - LFTs
  - RFTs
  - ANA

How will you treat this patient?

The indication of treatment is when platelet count <25000,-30000/mcL (25-30 x 10^9/L) or those with HX of significant bleeding should be treated while other patients should be monitored.

- **Steroids** →treatment of choice is a short course of prednisone (1mg/kg for 2 weeks and taper over 4-6 weeks (± intravenous immunoglobulin (IVIG) or anti D (win Rho) depending on the severity).Additionally, a short course of high dose dexamethasone (40mg/day for 4 days 2-4 weeks for 4-6 times) is also an option for initial treatment. treatment . corticosteroids may takes 3 to 7 days for response and 66% will respond to steroid but will relapse on tapering while 33% will show long-term response and only 10-20% ll have long term remission after steroid withdrawal
- **Intravenous immunoglobulin (IVIG)** it is also 1st line treatment depending on the severity of ITP. it dose is 1g/kg IV for 2 days and response is seen typically within 24-336 hours

Scanned with CamScanner

- **Anti D** also indicated as first line treatment and should be given as single intravenous dose of 75mcg/kg. Additionally , IVIG and anti D can be repeated after 2 weeks if ITP is refractory to the first dose
- **Platelets transfusion** can be given simultaneously if there is an active bleeding
- **Anti-CD20 (Rituximab)** may be given as first line therapy in combination with steroids. Dose is 375mg/m^2 IV weekly for 4 weeks and leads to 50% response in steroids refractory ITP

2nd line treatment option (relapsed or refractory ITP)

Patients with a persistent platelets count <30000/mcL (30 x 10^9/L) or significant bleeding are candidates for 2nd –line treatment. 2nd line treatment include IVIG, anti-D , rituximab and the following drugs

- **Thrombopoietin Receptor Agnosits (TPO-mimetics).**There are three approved thrombopoietin receptor agnosits namely Romplostin (1mcg/kg SC weekly) , Eltrombopag (25-50mg orally daily) and avatrombopag (20mg daily) as 2nd line agents in ITP that have not responded to steroid , IVIG and even splenectomy
- **Syk** inhibitor (Fostamatinib 100mg BD) .it is recently indicated for ITP patients who are refractory to steroids , rituximab and TPO-mimetics
- **Splenectomy** →indicated in patients who are refractory to 2nd line treatment and result in 2/3rd will achieve a normal platelets counts .Patients should be vaccinated against the three encapsulated organism at least 2 weeks before splenectomy. Laparoscopic splenectomy is the preferred option
  - If patients still non-responsive then either search for an accessory spleen by PET-Scan and if negative start the patients on immunosuppressive therapy like MMF, azathioprine etc.
- **Autologous Stem Cell Transplantation** if the patient is refractory to all measure then this this the last resort
- **What are indications of platelets transfusion in ITP?**
- Bleeding regardless of the count
- When platelets counts are less than 10K
- DIC/sepsis when platelets counts are < 30K (Target is >10 K)

ITP and pregnancy

Definition of relapse, persistent and chronic ITP

- **Relapse ITP**→ when ITP flare-up after 3 months of treatment
- **Persistent ITP**→ no improvement in platelets after 3 months of treatment
- **Chronic ITP** → no improvement after 1 year of treatment

Platelets target in pregnancy

- 1st trimester → more than 10K
- 2nd trimester → more than 30K
- 3rd Trimester particularly near term whether vaginal delivery C-section→ more than 50K

Treatment options

Scanned with CamScanner

Steroids like moderate dose of prednisone and intermittent IVIG infusion are the preferred treatment option and while for refractory cases splenectomy is performed in the first or more safely in the 2nd trimester .TPO-mimetics are not safe in the pregnancy

Miscellaneous Bleeding Disorders

1. Haemophilia

Types

- Haemophilia A→ due to lack of factor VIII (most common)
- Haemophilia B(Christmas disease) → due to lack of factor IX
- Haemophilia C→ XI deficiency

It is X-linked recessive disorder and intrinsic coagulation pathway is defective in haemophilia characterized by inability to form a functional tenase complex to activate factor X to factor Xa . Severity of bleeding depend on the severity of deficiency of the factors

Investigations

- **APTT**→ prolong
- **Mixing study** →(patient plasma is mixed with normal plasma and aPTT is repeated) correction of aPTT
- **Plasma factor VII and IX assay** → **below normal**
- However , bleeding time , PT and thrombin time is normal

Treatment

- Factor VIII and IX replacement is the mainstay of treatment (frequency of transfusion depend on the severity of the disease and may range from 3 times/week to just infusion prior to high-risk activities like sports) .10-15% develops factors inhibitors (antibodies that interfere with factors activity and half-life) . we quantify the inhibitors and
  - if it is low titre (less than 5 Bethesda units BU) then we just increase the dose of infusion factors
  - and if it is >5BU then we have the following options of treatment
    - infusion of activated prothrombin complex concentrate or recombinant factor VII
    - inhibitor –tolerance induction (where high dose of factor VIII 50-300 units are given for 6-18 months and this result in 70% improvement in haemophilia A and 30 in B but in haemophilia B this may also cause nephrotic syndrome and anaphylaxis
    - **Emicizumab (fuse factor XI and X together, Recent Advances)** indicated to prevent or ↓ reduces the frequency of bleeding episodes for haemophilia A with or without Factor VIII inhibitors
- DDAVP(desmopressin) in mild cases of **haemophilia A**
- Antifibrinolytic agent like tranexamic acid for mild mucosal bleeding
- FFP is the mainstay of treatment for haemophilia C when factor XI is not available

2. Von Willebrand, s Disease

Scanned with CamScanner

Most common inherited disorder of bleeding and most cases are inherited as autosomal dominant and characteristically present like platelets disorder like epistaxis and menorrhagia. Normally von Willebrand factors binds to the collagen of the endothelium of the blood vessels and to the GPIb platelets receptor during platelets adhesion and promote platelets adhesion to the damaged endothelium. This is impaired in the von Willebrand disease.

Types

- Type 1 → partial reduction in vWF activity and is the most common type
- Type 2→ abnormal form of vWF
- Type 3→ total lack of vWF and inherited as autosomal recessive and is the most severe form

Investigations

- **bleeding time** → prolong
- **CBC** →platelets counts is normal in type 1
- **APTT** may be prolonged/slightly prolonged (in 50% of patients).
- **Factor VIII** levels(activity) may be mild/moderately reduced (much in haemophilia A) and is the most useful test for assessing the bleeding tendencies
- **VWF levels:** are variable and can be influenced by a number of factors, therefore, a single level of vWF within the normal reference range does not exclude the diagnosis of VWD.
- **VWF antigen** concentration in plasma: detected by quantitative immunoassay or ELISA, it is variably reduced, and also can be normal.
- **VWF activity** the degree of platelet agglutination is proportional to the concentration of vWF in the plasma, it is reduced in vWD.
- **Defective platelet aggregation with ristocetin:** Ristocetin is an antibiotic that causes VWF to bind to and activate platelets, platelets rapidly agglutinate in response to ristocetin, but the presence of vWF is necessary for this reaction to occur.
- **PFA-100:** it has 95% sensitivity to diagnose VWD.

Treatment

- Desmopressin (DDAVP) → (this increase 2-7 times the level of vWF by induces the release of Von Willebrand from Weible –Palade bodies of the endothelium and also raises level of factor VIII) is indicated for mild type 1 and some cases of type 2 . DDAVP dose is OD and no more 5 doses /week due to dilutional hyponatremia and allergic reaction
- vWF-containing factor VIII concentrate (intermediate purity) 60-80units/kg is indicated when bleeding is not controlled with DDAVP
- tranexamic acid for mucosal bleeding
- cryoprecipitate is no longer indicated

Scanned with CamScanner

3. Disseminated intravascular Coagulation (DIC)

Characterized by low platelets, microvascuar haemolysis, fluctuating neurological signs, renal impairment and fever.

Causes of DIC

- Malignant disease
- Septicaemia (e.g. Gram-negative, including meningococcal)
- Haemolytic transfusion reactions
- Obstetric causes (e.g. abruptio placentae, amniotic fluid embolism,pre-eclampsia)
- Trauma, burns, surgery
- Other infections (e.g. falciparum malaria)
- Liver disease
- Snake bite

International Society on Thrombosis and Haemostasis (ISTH) Diagnostic Scoring System for DIC

Parameter	Score
Platelet count	> 100 ×10 ^ 9 / L = 0 < 100 ×10 ^ 9 / L = 1 < 50 × 10 ^ 9 / L = 2
Elevated fibrin marker (e.g. D-dimer, fibrin degradation products)	No increase = 0 Moderate increase=2 Strong increase=3
Prolonged PT	<3 s = 0 >3 s but <6 s = 1 > 6 s = 2
Fibrinogen level	> 1g / L = 0 >1g / L = 1
Calculate score: >5 compatible with overt DIC: repeat score daily, <5 suggestive of non-overt DIC: repeat next 1-2 days	

Management of DIC

- Assess for underlying cause of DIC and treat.
- Establish baseline platelet count, PT, aPTT, D-dimer, fibrinogen.
- Transfuse blood products only if on-going bleeding or high risk of bleeding.
  - **Platelets**→ target value is > 20,000/mcl (20 x 109/L) in most patients) or >50,000/ mcL (50 × 109/L) in severe bleeding, eg, intracranial haemorrhage)
  - **Cryoprecipitate**→ to keep the fibrogen level > 80-100mg/dl

Scanned with CamScanner

- **FFPs**→ to maintain normal or near normal (<1.5 times normal) PT and aPTT
- **Packed red blood cells** → to maintain HB >8 g/dl
- Follow platelets, aPTT, PT, fibrinogen level every 4-12 hours
- Follow laboratory parameters every 4-12 hours as clinically indicated until DIC resolves
- If there is persistent bleeding due to severe consumption or consumption that requires excessive blood product, consider use of heparin (initial infusion, 5 units/kg/h) and titrate to desired clinical goals; do not administer bolus
- For HUS→ FDA approved two monoclonal antibodies for treatment of HUS eculizumab and ravulizumab

4. Heparin –Induced thrombocytopenia (HIT)

Diagnosis of HIT is made when new-onset thrombocytopenia a is detected in a patient within 5-14 days of initial exposure to heparin .It occurs in 3% of unfractionated heparin and 0.6% of patient exposed to lower –molecular –weight heparin

Investigations

- CBC→ decline of 50% platelets count is expected
- 4T score (Google it)→ low 4T score is predictive of excluding HIT
- Screening PF4-heparin antibody test. If the PF4-heparin antibody ELISA is positive, then
- Serotonin release assay(SRA)

Types

TYPE 1 →

- Non-immune
- Occours soon after the administration of heparin eg within two days
- Self-limiting and platelets improve with continued heparin administration

Type 2→

- Immune mediated
- It is prothrombotic condition despite being associated with low platelets
- Typically occours 4-10 days after heparin therapy
- More severe than type 1

Treatment

- Immediate discontinuation of all forms of heparin
- Due to a high risk of thrombosis in HIT patients, an alternative anticoagulant should be initiated. Argatroban or bivalirudin (direct thrombin inhibitor) is preferred in critical illness because of the shorter duration of action while fondaparinux (anti-Xa inhibitor) for initial treatment of HIT is a in clinically stable patient.
- For confirmed HIT,an anticoagulant agent should be continued until the platelet count has raised to at least 100,000/mcL where treatment with a warfarin (vitamin K antagonist) may be initiated.
- In patients with HIT, some form of anticoagulation (warfarin or other) should be continued for at least 30 days, due to a persistent risk of thrombosis even after the platelet count has recovered, and 3-6 months in patient with documented thrombosis

Scanned with CamScanner

- Exposure to heparin should be avoided in all patients with a prior history of HIT, if cant not be avoided due to a procedure, it should be with- held until PF4-heparin antibodies are no longer detectable

5. Evan Syndrome

It is warm AHA and thrombocytopenia .it is treated with IVIG, steroid and followed by immunomodulating therapy

6. Qualitative platelets disorder

- **Bernard –Soulier Syndrome** (absence of GPIb/IX/V complex that is a receptor for vWF) .treatment is supportive like tranexamic acid, DDAVP may be useful in some cases and recombinant activated factor VII. in all cases anitpaletelts drugs like aspirin should be avoided
- **Glanzmann Thrombasthenia** (absence of aIIbß3 also known as GpIIb/IIIa). Platelets transfusion is the standard treatment and patient should receive leukocyte –depleted blood product .Additionally patient should be vaccinated for HBV. **Recently FDA approved** rFVIIa for patients with bleeding refractory to platelets transfusion.

written by Aiman Usman Lodhi (neurology Resident HMC Peshawar)

Scanned with CamScanner

NEUROLOGY

Contributed By: Dr Aiman Usman Lodhi (Resident HMC Peshawar)

APPROACH TO STROKE

P/C

One –sided body weakness

HOPI (ODPARA-V)

My patient who is known case, mentioned risk factors (like DM, HTN, smoking, atrial fibrillation) presented with (RT/LT) body weakness that is sudden in onset, 1-2 days in duration and non-progressive in nature .Patient describe his weakness as loss of power in RT sided body involving upper and lower limbs and he is unable to move the affected part of the body. However, there is no HX of numbness, pain; needle like sensation and abnormal sensation .Additionally, there is no HX of double or loss of vision, facial asymmetry, difficulty in swallowing & speaking. hearing and breathing. The weakness is non-flucating, persists throughout night and day, and has no reliving and exacerbating factors. The weakness is not preceded by sudden excruciating headache followed by altered sensorium, jerky movements of body, neck stiffness & high-grade fever, early morning headache, visual disturbance, HX of urinary and faecal incontinence, change in the personality and memory.

Now exclude D/ds of stroke (Stroke mimics)

- **Trauma** → no HX of head injury , trauma and fall
- **Post –epile[illegible] Todd paresis** → HX of fits followed by weakness of the body
- **Multiple sc[illegible]osis**→ HX of visual disturbance and weakness that is improved spontaneously
- **SOL**→ HX of headache that is worse in early morning associated with body weakness
- **Cerebral abscess** →HX of high grade fever , ear discharge associated with altered sensorium and weakness
- **Migraine** → HX of headache that is associated with nausea /vomiting and worse with light and noise
- **Hypoglycaemia**→ HX of low blood sugar /HX of episodic sweating, palpitation and blurring of vision
- **Meningoencephalitis** → HX neck stiffness , high grade fever and change in the behaviour
- **Conversion disorder**

CARE/RECA of the stroke

Ischemic stroke risk factors

Ask about important risk factors like

- DM, HTN, smoking, dyslipedemia , heart problems(rheumatic heart disease, valve replacement, IE and atrial fibrillation) DST(recent childbirth) , vertebral or carotid dissection due to trauma , infection(HIV , syphilis and TB) ,autoimmune disorder(behcets, SLE and antiphospholipid syndrome) , vasculitis (GCA and Takayasu arteritis)

Scanned with CamScanner

- Hypercoagulable state like family HX of blood clotting , HX of blood thinning medication , lumps and bumps (malignancy) , haematological (Polycythaemia , MCGUS ,PNH and sickle cell disease) , homocystinuria, OCP&HRT and nephrotic syndrome

Haemorrhagic stroke risk factor

- Trauma
- Subarachnoid haemorrhage(worst headache of life)
- Bleeding disorder
- Anticoagulant (HX of blood thinning medication
- Amyloid angioapthy
- AV malformation
- Substance abuse (alcohol , cocaine and amphetamine)

Complications of stroke

- Aspiration pneumonia (or recurrent chest infection)
- Fits and altered sensorium
- Depression and anxiety
- UTI (Burning micturition)
- Bedsores and skin rash
- DVT and PE due to prolong immobility
- Contractures
- Constipation and or diarrhea

Now ask about relevant
ITP and
PAM-HUGS-FOSS-TV-F

Examination

Vitals

- **GPE** →consciousness level, face, posture, walking aids and physique
- **CNS** → upper and lower limbs for tone, power, reflexes and all modality of sensation, gait cortical and higher mental function like speech, cranial nerves and visual filed , signs of meningeal irritation(neck rigidity and kerning sign) and fundascopy (DM and HTN changes)
- **CVS** →murmur , pulse (irregular) and carotid bruit
- **Resp** → look for aspiration pneumonia (LRTI)
- **Abdomen** → not significant

Scanned with CamScanner

VIVA OF STROKE

35 years old male office worker, with sedentary lifestyle and a smoker who smokes ten cigarettes per day for last 10 years (i.e 5 pack years) presented in emergency with sudden onset of right sided weakness with slurred speech. He has never experienced such symptoms in past. On examination, his speech was slurred. GCS E4M6V4 14/15 , Tone was increased in right upper and lower limb with power of 0/5 in both limbs. However, 5/5 on left side. Reflexes were ++ on right side. Pronator drift was noted as well. Right side babinski positive. Rest of the systemic examination was normal. CT brain plain showed no acute changes. NIHSS scoring was done which were 14 so, he was proceeded for thrombolysis with Alteplase.24 hour post thrombolysis CT BRAIN was repeated according to thrombolysis protocol which showed hyopodensity in the left temporopariteal region.

What are the causes Of stroke in Young Patient?

INFECTIONS:

- HIV
- Fungal meningitis
- Tuberculous meningitis
- Varicella zoster infection
- Lyme disease
- Neurosyphilis
- Vasculitis of the CNS
- Neurosacroidosis
- Neurocysticercosis
- Wegners Granulomatosis
- Sjogren Syndrome
- Kawasaki disease

BLOOD RELATED DISORDERS (HEMATOLOGIC CONDITIONS)

- Protein C and S Deficiency
- Antithrombin deficiency
- Anabolic steroids
- Erythropoetin
- Harmonal Oral contraceptives
- Nephrotic syndrome
- Sickle cell disease
- Pregnancy
- Cancer
- Homocysteine related disorder
- Antiphospholipid syndrome
- SLE
- Lymphoma
- Leukemia

Scanned with CamScanner

NON-ATHEROSCLEROTIC ANGIOPATHIES:

- Cervical artery dissection (tear in carotid or vertebral artery)
- Fibromuscular dysplasia
- Migrane induced stroke
- Reverible cerebral vasoconstriction syndrome
- Susac syndrome (microangiopathy with triad of Encephalopathy, Hearing loss, retinal artery occlusion)
- Sneddon syndrome (hypertension, livedo reticularis, TIA / stroke)

GENETIC CONDITIONS:

- Marfan syndrome
- Sturge weber syndrome
- Neurofibromatosis
- Fabry disease
- CADASIL (Cerebral autosomal dominant arteriopathy with subcortical infracts and leukoencephalopathy)
- Von Hippel Lindau
- Pulmonary Arteriovenous Malformations
- MELAS syndrome
- Hereditary Hemorrhagic Telangiectasia

OTHERS:

- Smoking
- Obesity
- Drug abuse (cocaine , amphetamine)
- Traumatic injuries
- Valvular heart disease
- Infective endocarditis
- Hypertension
- Diabetics

How will you investigations this patient:

- **MRI BRAIN with DWI image** (to identify patients with wake-up stroke or unknown stroke onset time) new onset of stroke is positive on DWI but negative on FLAIR sequence.
- Angiography of head and neck (MRA /CTA)
- ECG
- ECHO (transoesophgeal)
- Blood tests :
- CBC
- Metabolic profile

Scanned with CamScanner

- ESR
- CRP
- Lipid profile
- TSH
- Toxicology (cocaine / amphetamine)
- Homocysteine levels
- Troponin
- APTT/PT/INR
- Hypercoagulable profile screening (should be done 2 weeks after ischemic event due to consumption of clotting factors)
- Genetic studies e.g gene mutation in cases of suspected syndromes or family history

What is Bamford stroke classification?

MANAGEMENT OF STROKE IN YOUNG:

ACUTE MANAGEMENT:

In case of acute ischemic stroke, patient comes in window period which is 3-4.5 hours. Such patients should be proceeded for thrombolysis with alteplase after NIHSS Score

- 0-4: conservative management (however if disabling symptoms are present that can halt quality of life of the patient then thrombolysis should be considered as well.)
- 5 and above : proceed for thrombolysis

Dose of alteplase is 0.9mg/kg (10% bolus in one minute and rest of the dose in one hour)

Antiplatelet and statin after 24 hours after repeating CT brain and ruling out hemorrhage in thrombolysed patient.

It is advisable to monitor blood pressure and glucose levels with other vitals. Blood pressure must not be lowered abruptly in 24 hours, no more than 25 percent is recommended as it can further damage the penumbra of the ischemic area. If BP is > 220/120 it should be reduced 25% in 2-3 hours and if BP <220/120 with no on-going end organ damage ,BP should not be lowered

What is a thrombolysis Inclusion and exclusion criterion?

Inclusion Criteria:

Ischemic stroke patients with onset of symptoms less than 3-4.5 hours.

A deficit measureable on NIHSS.

Baseline CT brain that showed no evidence of infraction or intracranial hemorrhage.

Exclusion Criteria:

- History suggestive of intracranial bleeding risk or past history of CNS bleeds
- Recent history of subarachnoid hemorrhage, head trauma, AVM, aneurysm or cranial or intraspinal surgery within last 2 months.
- Rapidly improving symptoms.
- Blood glucose <50 or > 400mg/dl.

Scanned with CamScanner

- History of head trauma within previous 3 months.
- History of major surgery within 14 days.
- Recent or concurrent MI.
- Patient has received heparin or anticoagulation therapy
- Pregnancy
- INR>1.7
- Platelets below one lac.
- Systolic BP> 185 or diastolic BP > 110 (BP needs to lower down before giving thrombolytic therapy)
- History of seizure at onset of symptoms (relative exclusion due to Todds palsy)
- Advanced kidney disease or liver failure

What do you know about National Institute of Healthh Stroke Scale/ Score (NIHSS)?

Scoring system that quantifies stroke severity on neurological examination.
Scoring devised to make decision for thrombolysis in case of acute ischemic stroke.
Total points: 42

SCORE	STROKE SEVERITY
0	no stroke
1-4	minor stroke
5-15	moderate stroke
16-20	moderate to severe
21-42	severe stroke

Scanned with CamScanner

NIHSS ELEMENT	NIHSS SCORE	
Level of consciousness Arousal status	Alert (awake or awaken easily)	0
	Drowsy (responds but falls back	1
	Obtunded (response only to pain)	2
	Comatose	3
Loss of consciousness Ask about month / age	Both questions answered correctly	0
	One answer correct	1
	Unable to answer both	2
Command Open/close eyes Open/close hands	Follows both	0
	Follows one	1
	Follows none	2
Eye movements (Horizontal)	Normal	0
	Mild gaze paralysis	1
	Complete gaze paralysis	2
Visual fields	Normal	0
	Partial hemianopia	1
	Complete hemianopia	2
	Bilateral hemianopia	3
Facial movements	Normal	0
	Minor paralysis	1
	Partial paralysis	2
	Complete paralysis	3
Motor left arm	Normal	0
	Drifts downward not before 10 sec	1
	Drifts to bed within 10 sec	2
	Movement, but not against gravity	3
	Complete paralysis	4
Motor right arm	Normal	0
	Drifts downward not before 10 sec	1
	Drifts to bed within 10 sec	2
	Movement, but not against gravity	3
	Complete paralysis	4
Motor left leg	Normal	0
	Drifts downward not before 10 sec	1
	Drifts to bed within 10 sec	2
	Movement, but not against gravity	3
	Complete paralysis	4

Scanned with CamScanner

Motor left leg	**Normal**	**0**
	Drifts downward not before 10 sec	**1**
	Drifts to bed within 10 sec	**2**
	Movement, but not against gravity	**3**
	Complete paralysis	**4**
Motor right leg	Normal	0
	Drifts downward not before 10 sec	1
	Drifts to bed within 10 sec	2
	Movement, but not against gravity	3
	Complete paralysis	4
Limb ataxia	Absent	0
	Present in one limb	1
	Present in two or more limbs	2
Sensory (Hemisensory loss Test on arm and face)	Normal	0
	Mild to moderate loss	1
	Severe to total sensory loss	2
Language /aphasia (repetition and comprehension)	Normal ability to use words and Follow commands)	0
	Mild to moderate (repeat with Difficulty)	1
	Severe aphasia	2
	Mute	3
Dysarthria (slurred speech)	Normal speech	0
	Mild to moderate slurred	1
	Severe	2
Neglect (ignores touch or vision to one side)	No abnormality	0
	Mild	1
	Profound	2

Scanned with CamScanner

What is conservative / long term management?

Goal is to reduce disability, prevent complications and recurrence.

- **Antiplatelet:**

Loading dose 300mg aspirin for 2 weeks then single or dual antiplatelet lifelong depending upon indication

Aspirin can be given per rectal in cases patient is NPO or no NG available.

- **Statin :**

Start after 24 hours of event. Continue lifelong therapy

Use with caution in liver disease.

For chronic liver disease : dose adjustments needed with rosuvastatin and pravastatin.

Atorvastatin: safe in kidney disease

Other care in long term:

- Physiotherapy to prevent contractures, limit disability and to regain muscle strength. Chest physiotherapy in case of aspiration.
- Nutrition
- NG feed to prevent aspiration pneumonia.
- Speech therapy for speech related issues.
- Posture change every 2 hours to prevent pressure sores plus use of air mattress.
- Prophylaxis to prevent DVT and pulmonary embolism.

- **Indications for single antiplatelet:** ASPIRIN 162-375mg daily

Low risk TIA (non- cardio embolic origin), ABCD2 score < 4

Ischemic stroke of moderate severity, NIHSS >5

- **Indications for dual antiplatelet: Aspirin Plus Clopidogrel**

High risk TIA (Cardio embolic Origin), ABCD2 score 4 or > 4

Major stroke (large vessel occlusion) NIHSS 5 or < 5

Other antiplatelet in case of allergy to aspirin and clopidogrel: tirofiban, ticagrelor, cilostazol.

Surgical treatment of stroke

1. **Carotid Artery Revascularization:**

In cases of carotid artery stenosis more than 70 percent.

Staged revascularization of each carotid artery is advised to prevent bradycardia and cerebral hypoperfusion. One carotid at one time principle.

It is advisable to continue single antiplatelet life long after procedure.

2. **Mechanical Thrombectomy:**

In cases of large artery occlusion and should be done within 24 hours despite if they received thrombolytic therapy or not.

Management in case of stroke with atrial fibrillation:

Scanned with CamScanner

Anticoagulants: recommended for secondary stroke prevention.

Anticogulants are given after 2 weeks as there is risk of bleeding in cases of large size infract , however in small to moderate size infract it can be started after 48 hours.Anti-coagulation with warfarin or a direct oral anticogulants (DOACS).

Warfarin is given in cases of mechanical heart valve to prevent cardioembolic stroke with target INR 2-3.

ENOXAPARIN 1mg/kg BD low molecular weight heparins may be used as an alternative to intravenous heparin in patients with acute stroke when early anticoagulation is desired to prevent recurrent stroke

Lifestyle modifications:

Ssmoking cessation, exercise, weight reduction for patients with obesity and balanced diet.

Special circumstances

- Stroke due to IE RX → antibiotics only as it is due to septic emboli
- Prosthetic Mechanical valve → aspirin and warfarin with monitoring of INR
- HIV stroke → ART and aspirin
- Sickle cell induced stroke → Exchanged transfusion
- Stroke with MI /LV thrombus →offer anticoagulation for 3 months and then reassess

What is reversible ischemic neurological deficit?

It mean neurological deficit that persist for > 24 hours but recovers totally within a week

What is stroke –in-evolution?

It means the neurological deficit worsens gradually or in a stepwise fashion over hours or days

Haemorrhagic stroke

- SAH
  - Traumatic (most common cause)
  - Non-traumatic

Investigation

- CT brain plain >MRI
- CSF→ xanthochromia
- CT angiography

What is HUNT-HESS SCALE?

RX

- Conservative treatment like seizure prophylaxis , mannitol and Dexa to reduce the intracranial pressure
- Control BP ≤140/90
- Clipping and coiling

Scanned with CamScanner

- Treatment of complication like vasospasm with nimodipine 60mg 4 hourly for 21 days , shunting in case of hydrocephalous

- **Intracerbral bleed (ICH)**
- Commonest site basal ganglia and cause is HTN while other cases include cerebral amyloid angioapthy ,SOL , blood thinning medication and AVM

Treatment

- Target BP < 140/90
- Treat the cause like FFPs and prothrombin complex concentrate and vit-k for warfarin induced massive bleed

Indication of surgery in haemorrhagic stroke

- Cerebral bleed > 3cm
- Hydrocephalous
- Brainstem compression

Calculation of volume of ICH on CT

$$\frac{A \times B \times C}{2}$$

- A→ max length in CM
- B→ Max width
- C→ no of slices x slice thickness /2

A-Fib and haemorrhagic stroke

- ICH in patient already on anticoagulant→ restarts after 4-8 weeks
- If patient is not on anticoagulation and cause of A-fib cannot be treated than LA appendage occlusion

Also read neurology short cases section for stroke for additional points

Scanned with CamScanner

APPROACH TO PARAPLEGIA/PARAPARESIS (Flaccid and Spastic)

HOPI (ODPARA-V)

Patient presented with weakness of lower limbs that is sudden in onset, progressive in nature and 2-3 days in duration .patient described weakness as lack of power and felling stiffness and tightness (spastic)/or floppiness (flaccid) in the lower limb. Lower limbs were involved simultaneously .Now state whether other part of the body involved or not, ascending or descending in nature, persistence of weakness throughout day or night , any reliving and exacerbating factors and degree of impairment of his daily life activities

- Ask about facial weakness, difficulty in voice, change in the character of voice and nasal regurgitation of food content and numbness. Headache that is worse in the morning and change in the vision (parasagittal meningioma)
- Involvement of bowel and bladder ,palpitation , sweating and racing of heart during rest
- Preceding HX of vaccination , loose motions and sore throat

If patient, give HX of spastic Paraparesis, first exclude imp DDs of spastic Paraparesis followed by few important DDs of flaccid Paraparesis (and vice versa), as we cannot differentiate confidently both based on just HX.

DDs of Flaccid Paraparesis

- **GBS** → HX of sore throat and loose motions 2-3 weeks preceded the weakness
- **CIDP** → HX of weakness that is waxing and waning over period of time
- **Hypokalemic Periodic Paralysis** → HX of carbohydrate rich diet , exertion and sweating
- **Thyrotoxic periodic paralysis** → HX of heat and cold intolerance
- **Botulism**→ HX of double vision , difficulty in swallowing followed by weakness of lower body
- **Lime disease** → HX of forest visit , skin rash and tick bite
- **Diphtheria**→ HX of sore throat , whitish membrane on oral cavity that bleeds on stripping
- **Acute intermittent porphyria** → HX of recurrent abdominal pain , fits and red discoloration of urine on standing
- **Lead poisoning**→ HX of occupational exposure to lead , painting and residency in old rusted houses
- **Progressive muscular atrophy (MND)** → progressively increasing weakness over periods of months to years
- **NMJ disorder like myasthenia gravis and other myopathies** → HX of fluctuating muscle weakness at the end of the day
- **Drug induced muscle weakness** → HX of prolong ingestion of alcohol , statin and steroid
- **Spinal shock** → Hx of trauma to the spine
- Now exclude few imp DDs of flaccid Paraparesis

Scanned with CamScanner

DDs of Spastic Paraparesis

4TS

- **Spinal trauma**→ HX of fall , trauma to the vertebrae
- **Spinal Tumor (primary or metastatic**→ HX of weight loss , decreased appetite and lumps and bumps
- **TB Pott,s disease** →contact HX of TB , nights sweats and fever
- **Transverse myelitis** → Hx of numbness upto …and loss of power preceded by HX of infection
- **MS**→ HX of transient blurring of vision and weakness
- **Syringomyelia**→ HX of loss of pain and temperature sensation in upper limbs, wasting of the small muscle of hands followed by weakness of the lower limbs
- **HIV** → HX of high risk sexual behaviour , IV drug abuse
- **Spinal abscess**→ localized tenderness and HX of high grade fever with rigors and chills
- **Motor Neuron disease** → HX of pure motor weakness that is progressive and without loss of any sensory modalities
- **SICD(Vit B12)**→ paleness of complexion and difficulty in walking and memory impairment
- **Fredric ataxia** →HX of difficulty in walking ,high arch feet and anatomical deformity of the vertebral column
- **Cervical myelopathy** → pain in the shoulder and neck that may be preceded by trauma
- **Hereditary spastic Paraparesis**→ family HX of weakness in the lower limb
- **Anterior spinal artery infarction** →HX of DM, dyslipedemia and irregular pulse
- **Multiple myeloma (spinal cord compression)** → HX of paleness of complexion , back pain and constipation
- **Taboparesis** →HX of painless joint deformity that is preceded by painless genital ulcers
- Exclude few imp DDs of flaccid Paraparesis

DDs of Quadriparesis

- Cervical myelopathy
- Syringobulbia
- MND ,
- MS
- Cervical tumor or trauma
- B/L stroke

Scanned with CamScanner

Examination scheme of GBS

Vitals (pulse tachycardia) and check orthostatic hypotension

GPE → look for CVP and site for any complication, SOB,

- Standard neurological examination (flaccid paralysis/paresis), reflexes absent , sensation intact , check cranial nerves and bowel and bladder
- CVS →orthostatic hypotension , and look for other signs of autonomic involvement like resting tachycardia
- Resp →look for SOB and resp muscle involvement

Guillain- Barre Syndrome: autoimmune demyelinating disorder where immune system attacks peripheral nervous system (somatic and autoimmune) and cranial nerves.

30 years old male presented with complaints from past 2 weeks that include progressive symmetrical loss of power in lower limbs which now progressed to upper limbs as well. He had episode of lower respiratory tract few days back after which he got gradual loss of power in lower limbs that now have progressed to upper limbs as well. He was having shortness of breath and nasal regurgitation of food and dysphagia to liquids as well. He was unable to close his eyes and his sleep was disturbed as well. On examination, tone in all limbs was flaccid. Power was 0/5 in lower limbs and 2/5 in upper limbs and weak neck extension as well. Reflexes were diminished in all limbs. Sensations were intact. There was no bowel bladder involvement. Gag was not intact. Cough reflex was weak. Bilateral lower facial palsy noted as well with up rolling of eyes. Single breath count was up to 8. Blink reflex test positive. Patient was shifted to intensive care unit for ventilatory support and plasmapheresis was started meanwhile. After 5 sessions patient condition improved with vigorous sessions of physiotherapy. He was off ventilatory support and power in upper limbs improved to 4/5 however , 3/5 noted in lower limbs .Speech and swallowing muscles were still weak after assessment so NG feeding was advised for next 2 weeks with follow up in OPD and physiotherapy at home.

Differential Diagnoses:

- **Muscle Disease:**
- Dermatomyositis
- Polymyositis
- Periodic paralysis (hypokalemia, hyperkalemia)
- Acute viral myositis
- Acute rhabdomyolysis
- Myopathy associated with critical illness

Neuromuscular Disorders:

- Use of Neuromuscular blockers e.g succinylcholine

Scanned with CamScanner

- Botulism
- Myasthenia gravis
- Spinal Cord Disorders:
- NMOSD
- Compressive Myelopathy
- Poliomyelitis
- Transverse myelitis
- Anterior spinal artery syndrome

Brain Disorders:

- Posterior fossa structural pathology
- Cerebellar ataxia
- Bilateral strokes
- Acute demyelinating encephalomyelitis (ADEM)

Peripheral Nervous System Disorders:

- Diphtheria
- CIDP
- Lyme disease
- Thiamine deficiency
- HIV related radiculopathy
- Porphyria
- Tick paralysis
- Toxin induced neuropathy (arsenic)
- Hypoglycemia and hypophosphatemia induced neuropathy
- Substance abuse (n-hexane exposure from glue sniffing)
- Lymphoma
- Sarcoidosis

What Are The Variants Of GBS?

Common:

- AIDP (acute inflammatory demyelinating polyneuropathy)
- AMAN (Acute Motor Axonal neuropathy) .associated with Compylobacter Jejuni
- AMSAN (Acute Motor Sensory Axonal neuropathy) . Have mild sensory symptoms like paresthesia

Rare:

- Miller Fischer Syndrome (MFS) associated with GQ1b antibodies.
- Pharyngo cervical brachial variant
- Acute panautonomic neuropathy
- Bickerstaff encephalitis (ataxia ,hypersomnia and toxic look)

DIAGNOSTIC CRITERIA: Modified criteria devised by National Institute of Neurological Disorders and Stroke (NINDS) is used which includes the following; Global areflexia in weakened limb

Scanned with CamScanner

Progressive weakness of limbs ranging from mild weakness to paralysis with involvement of trunk, bulbar and facial muscles involvement, and external opthalmoplegia

Supporting points;

- Duration of symptoms progression over days to four weeks
- Symmetric bilateral symptoms
- Pain in the trunk or limbs
- Cranial nerve involvement
- Autonomic dysfunction
- Sensory dysfunction that is mild
- No fever
- CSF albuminocytologic dissociation
- EMG findings consistent with GBS
- Recovery period starting 2-4 weeks once disease progression is stopped.

Note: Another criterion known as Brighton criteria is also used for diagnoses of GBS.

Investigations:

- All baseline blood tests including serum electrolytes to check for potassium. (hypo or hyperkalemic periodic paralysis).
- Serum glucose
- Serum calcium
- Serum phosphate and magnesium
- (low levels of magnesium causes hypokalemia as well)
- ESR
- HBA1c

Electro Diagnostic Studies Gold Standard for Diagnoses

Performed to support diagnoses, check severity, monitor prognosis and rechecked on different intervals to look for recovery.

It can be normal in initial stage of disease. Changes are evident after three to four weeks. The findings include;

- F wave prolongation or absence
- Absence of H reflexes
- Prolonged distal latency
- Conduction Block
- Reduction of conduction velocity
- Needle EMG shows denervation in weak muscles

Facial NCS also support the diagnoses.

Sural sparing on NCS:

Unique footprint feature of GBS: Defined as absent/abnormal median or ulnar sensory nerve action potential (SNAP) amplitude with normal sural SNAP amplitude.

CSF STUDIES:

Scanned with CamScanner

Albuminocytologic dissociation: elevated protein with normal white blood cells i.e <5/l.

Antibody Testing:

Anti GQ1b levels are done in cases where miller Fischer and other rare variants of GBS are suspected.

Neuroimaging Studies:

MRI lumbosacral and cervical done to rule out local spinal pathologies . MRI brain done to rule out bilateral strokes and other central diseases mimicking GBS

MANAGEMENT:

Immunomodulatory Therapy:

Intravenous Immunoglobulin

Given to patients whose disease is progressing at faster rate or involvement of bulbar muscles and autonomic instability. It should be given in first 4 weeks of onset of symptoms.

For cases of MFS, immunotherapy is not advised except when autonomic instability or bulbar involvement is evident. As opthalmoplegia, ataxia and areflexia in MFS don't need immunotherapy and most patients improve itself in 6 months' time.

Dose and infusion protocol:

0.4g/kg per day for five days

Administration of 500ml normal saline, IV dimenhydrinate 25mg and Acetaminophen 500mg before infusion

Rate:

Started at 0.3ml-0.5/kg/hr and titrated till 6- 8ml/kg hr to avoid adverse effects.

Adverse effects of IVIGS:

- Anaphylactic reaction
- Nausea
- Hypotension
- Aseptic meningitis
- DVT
- Pulmonary embolism
- Kidney failure
- Stroke
- Cardiac arrest

Plasma Exchange or Plasmapheresis:

Alternative to IVIG. Usually 5 TO 7 sessions are done.

Both IVIGS and plasma exchange has same efficacy and whatever is available should be provided to the patient within 4 weeks of onset of symptoms for better recovery.

Side Effects of Plasma Exchange:

Intravascular access and line related infections

Sepsis

Hypotension

Scanned with CamScanner

Transfusion reactions

Prognosis and Recovery: Some patients after receiving IVIGS or plasma exchange show less improvement. However, with further follow-up over time these patients recover. Recovery may take upto one year with residual muscle weakness. In case of no recovery, reevaluate the case and think of other diagnosis.

Indications for ICU Care:

- Impending Respiratory Failure:
- Clinical signs of respiratory failure include
- shortness of breath while speaking or at rest
- use of accessory muscles of breathing
- Failure to count upto 15 in one breathe
- Rapid respiratory rate with tachycardia
- Abnormal ABGS
- FVC <15 to 20 mL/kg or <1L.(THIS IS USE TO MONITOR RESPIRATORY FAILURE .)

ERASMUS GBS RESPIRATORY INSUFFICIENCY SCORE PLUS MRC SUM SCORE:

These predict the rate of respiratory failure and need for ICU care in first week of hospital admission.

0-2: low risk

3-4: intermediate risk

5-7: high risk

Autonomic Instability:

It warrants urgent ICU care.

Intubation and Ventilatory Support:

Patients with impeding respiratory failure and bulbar dysfunction should be at once intubated without delay.

To weaning off from ventilator check muscle strength and do serial pulmonary function tests. If condition not improved till 2 weeks tracheostomy should be done.

Manage and look for complications like tracheostomy induced pneumonia and secretions blocking airways.

Autonomic Instability and Cardiovascular Complications:

Monitor for Tachyarrhythmia or Bradyarythmia and Other Arrhythmia like Atrial Flutter, VT, and Conduction Blocks Etc.

Hypotension;

Managed with IV fluids and low dose phenylephrine 0,1-1.5mcg/kg/min

Hypertension:

Mean arterial pressure > 125 mmHg should be treated with labetalol, nitroprusside, nicardipine.

Note: continuous telemetry with blood pressure monitoring is advised every 4 hours.

ILEUS:

Scanned with CamScanner

Neostigmine or methylnaltrexone can be used. Colonoscopy in case of treatment failure
Patient should not be left alone due to orthostatic hypotension.

DVT Prophylaxis:

Compressive stockings
Low molecular weight heparin
DOACS

Pain: *(due to inflammation of nerves and axonal degeneration)*

For neuropathic pain: pregabalin, gabapentin, carbamazepine
NSAIDS for somatic pain
Refractory cases: epidural morphine

Physiotherapy:

Limbs and chest physiotherapy

Nutrition:

NG feeding in case of bulbar involvement

Prevention of Bedsores:

Air matress and posture position change every 2 hours.

What are the poor prognostic factors of GBS?

- Age > 40
- Preceded by diarrheal illness
- Need for ventilatory support
- Poor upper extremity strength
- High anti-GM1 antibody titre

Cause of death

- Resp involvement
- Bulbar involvement
- Autonomic involvement (arrhythmias)

What is the natural HX of GBS?

- 85% recovers
- 15% residual deficit and
- 5 dies and 2.5-5% recurrent

Triggers like Infection (incubation period 1-3 weeks) → weakness that ↑ for 2 weeks and stable (plateau) for 4 weeks and if not treated then death and or disability
Reader is advice to also read GBS in neurology short case section

Hypokalemic Periodic Paralysis:

Autosomal dominant condition due to CACNA15/SCN4A mutation in Na Ca channels that is characterized by muscle weakness or even paralysis

35 year old female presented with complaints of sudden onset of all four limbs. She gave history of feeling fatigued and weakness in all limbs in past after strenuous exercise or consumption of carbohydrate rich food.

Scanned with CamScanner

But this time the condition started after the death of her brother (stress and emotional situation). She has issue of muscle cramps from long time and her sleep was disturbed. On examination, tone was flaccid in all limbs however pseudomyotonia was present as well . Global hyporeflexia was with symmetrical loss of power 2/5 in all limbs with intact sensations. Abdomen was tense, non-tender and distended. Pulse was regular however rate was 54 bpm. Rest of the examination was normal.

Differential Diagnoses:

- Myasthenia Gravis
- Paramyotonia Congenita
- Hyperkalemic or normokalemic periodic paralysis
- Anderson Tawil Syndrome
- Thyrotoxic Periodic Paralysis
- Guillian Barre Syndrome
- Secondary hypokalemia due to any GI , kidney or metabolic issue E.G RTA , diuretics, steroids , hyperalodstrenoism , cocaine binge, urinary potassium wasting .

Note: Normal serum potassium levels between attacks help distinguish primary hypokalemic periodic paralysis from other secondary causes of hypokalemic paralysis.

TRIGGERS:

- Cold
- Emotional stress
- Carbohydrate load
- Strenuous exercise

INVESTIGATIONS:

Baseline blood tests:

Serum electrolytes; K < 3.5mmol/l

Electro diagnostic Studies:

NCS & EMG:

Normal in acute attacks

NCS reveals reduced motor amplitudes at times of weakness.

Shows decline in CMAP (compound muscle action potential) amplitude and electrical silence that improves after potassium supplementation. There is reduced muscle fiber conduction velocity and increased polyhasic motor unit potentials.

Muscle Biopsy:

Done in some cases where it reveals single or multiple small vacuoles.

ECG: for any arrhythmia and bradycardia

Others: TSH, SERUM PHOSPHATE (it can also cause paralysis especially in DKA patients), serum magnesium, serum calcium, RFTs, ABGs, urinary electrolytes (potassium and chloride in spot urine are useful in differentiating renal and non- renal etiology for hypokalemia.

Gene Testing: Can also be done in cases where symptoms are suggestive of HPP.

Scanned with CamScanner

Provocative Testing: Done in cases where there is difficult to diagnose the disease due to fluctuation in serum potassium level.

Glucose Challenge Test:

Attack of hypokalemia is induced by giving oral glucose 2g/kg with insulin administration of 10 units subcutaneously. This test is generally not advised due to safety concerns.

Exercise Challenge Test:

Exercise on treadmill for 30 minutes induce weakness in muscles with decrease serum potassium levels. Monitoring potassium levels before and after event can give clue to make a diagnosis.

Administration of ACTH Analysis of muscle weakness and measuring potassium levels before and after ACTH is safest in these cases.

MANAGEMENT:

ACUTE:

Oral supplementation of potassium 60-120mEq of KCL in an incremental way or 30mEq of KCL is given every 30 minutes till the symptoms are improved.

Intravenous supplementation can be done if swallowing issues or GI upset like vomiting is present.

Best is to do cardiac monitoring while potassium replacement.

For IV supplementation of KCL dextrose should be avoided as it precipitates hypokalemia.

Mannitol is best vehicle for potassium.

LONG TERM/ PREVENTIVE MANAGEMENT:

Avoidance of precipitants.

Life style modifications such as low carbohydrate diet and avoiding strenuous exercise.

Carbonic anhydrase inhibitors:

Tab acetazolamide 250mg PO BD.

Or

Tab dichlorphenamide 25mg PO TDS.

Potassium Sparing Diuretics:

Tab spironolactone 100mg PO OD

Or

Tab Triamterene 150mg PO OD

How to calculate potassium deficit

(0.6 x Wt x 4- patients K level) is the patient deficit of K

If 20 mEq then one ampule and if 40 then 2 ampoule

- Peripheral line →10 mEq/hr
- Central line → 20 mEq/hr

10 mEq/hr in 100ml N/S /Hr and 40 mEq/ in 400ml/ over 4 hrs

Maintenance dose

0.5 mEq/kg

Potassium rich diet → dates, potatoes, tomatoes and banana

Oral potassium→ Neo-k and one tab Neo-k 500mg is equal to 6.7 mEq .

Scanned with CamScanner

Spastic Paraparesis/paralysis due to TM

Examination Scheme

Standard neurological examination
In Lower limb upper motor neuron signs, bowel and bladder dysfunction and loss of sensation of all modality if complete TM

Transverse Myelitis(TM): neuroinflammatory disorder of spinal cord.

55 years old male presented with complaints of postherpetic neuralgia (got herpes zoster 1 month back on front of the chest towards scapular region at the back) from past 3 weeks and now he got weakness in his lower limbs with 3 episodes of urinary retention and fecal incontinence from past 5 days. His vision was not disturbed. No speech and swallowing difficulty, shortness of breath or facial weakness. On examination, tone was increased in lower limbs; power was 1/5 in lower limbs but normal in upper limb. Clonus present in lower limbs with babinski positive. Sensory level present at T10 level

Differential Diagnosis:

- Trauma
- Ttuberculosis arachnoiditis
- Guillain-Barre syndrome

Compressive myelopathy:

- Disc herniation
- Vertebral body compression fracture
- Spondylosis

Vascular myelopathy:

- Dural arterovenous fistula
- Spinal cord infraction
- Epidural hematoma)

Metabolic myelopathy:

copper deficiency myeloneuropathy

- Vitamin B12 deficiency,
- Vitamin E deficiency

Neoplastic myelopathy:

- Astrocytoma, ependymoma
- Primary intramedullary
- Spinal cord lymphoma
- Metastatic disease

CAUSES:

- Idiopathic TM
- Post infectious:

Scanned with CamScanner

- ***Viruses:*** viruses may trigger an autoimmune reaction without directly infecting the spinal cord. Herpes including the one that causes shingles and chickenpox.
- CMV
- SARS -COV2
- EBV
- HIV West Nile
- Echoviruss
- Zika
- Influenzaa
- Hep B
- Mumps measles and rubella

Bacterial infections:

(Actinomyces. Pertussis, Tetanus, Diphtheria, Lyme disease, Syphilis, Tuberculosis)

Note:

Bacterial skin infections, gastroenteritis, and certain types of bacterial pneumonia also may cause transverse myelitis.

- **Parasites:**
- Echinococcus granulosis
- Taenia species
- Schistosomiasis species
- Trypanosoma species

Fungal infectio

- Coccidia
- Cryptococcus

Secondary infl atory conditions of CNS causing transverse myleitis

- Multiple sclerosis
- Neuromyelitis optica (Devic's disease)
- Autoimmune disorders (lupus, Sjögren's syndrome, and sarcoidosis)

Complications

People with transverse myelitis usually experience only one episode; however, transverse myleitis caused by other CNS conditions for e.g MS comes again as relapse. Patient lingers on with these complications;

- Pain
- Stiffness, tightness, or painful spasms (flexor spasms)
- Partial or total paralysis
- Sexual dysfunction
- Depression or anxiety

Scanned with CamScanner

DIAGNOSTIC CRITERIA:

- Sensory motor complaints attributable to the spinal cord
- T2 hyper intense signal change on spinal MRI
- Absence of compressive cord lesion
- Bilateral signs and/or symptoms
- Presence of sensory level
- Supporting investigations showing CSF pleocytosis and enhancement on MRI
- Neurologic deficit and progression between 4 hours to 21 days

Investigations:

Blood tests:

- ESR
- CRP
- Serum calcium
- ACE level
- HIV Serology
- HbsAg
- Lyme disease serology
- Dengue serology etc
- Vitamin B12 levels, vit E And

Selective investigations:

- Chest CT scans for sarcoidosis
- Salivary gland biopsy if high suspicion for Sjögren's disease but negative SSA/SSB antibody
- Neuro-ophthalmologic evaluation to look for evidence of optic neuritis
- Spinal angiogram in the setting of hyper acute myelopathies that are thought to be consistent with vascular event

Autoantibodies:

- Serum AQP4-IgG and MOG-IgG antibodies
- ANA
- Anti-ds-DNA
- Ro/SSA and La/SSB antibodies
- RA factor
- Antiphospholipid antibodies
- ANCA
- Paraneoplastic antibodies e. anti yu etc

IMAGING: Most important tool to diagnose TM and rule out other pathology mimicking transverse myelitis.

MRI Spine with Contrast:

T2 Signal changes in case of cord involvement corresponding to sensory level.
Rule out compressive myelopathy.

MRI Brain:

Scanned with CamScanner

Case of NMOSD, MS, ADEM. (All these are secondary causes of TM)

Spinal Angiogram:

If spinal infract is suspected due to hyper acute event.

CSF Studies: mainly done to look for infection causing TM

Cell count for infectious etiology (pleocytosis)

Glucose, protein (imp for diagnosis of TB, bacterial and fungal CNS infection causing TM)

CSF oliogoclonal bands for MS.

CSF culture and staining

Management:

Idiopathic TM: Acute

Without motor impairment: High-dose intravenous glucocorticoid treatment methylprednisolor (30 mg/kg up to 1000 mg daily) or dexamethasone (up to 200 mg) for three to five days.

TM with motor impairment: plasma exchange (PLEX) in addition to high dose intravenou glucocorticoid treatment on alternate days PLEX 5 sessions in 10 days duration; alternating wit methylprednisolone.

Progression despite steroids and PLEX: cyclophosphamide 400mg every 2 weeks for 1 cycles if needed.

Prevention of further Attacks: intravenous Rituximab 1gm every 6 months or ora mycophenolate 2 to 3 g daily.

Secondary demyelinating CNS disorders:

Acute attacks:

High dose intravenous steroids … methylprednisolone 1gm for 5-7 days. If severe motc dysfunction patient not improving start adjunct plasmapheresis.

Prevention of further attack associated with demyelinating CNS disorders like NMOSD, MS. Patient must be kept on low dose glucocorticoids and immunosuppressive medication to prever relapse.

TM due other systemic autoimmune disease:

Short course of high-dose intravenous glucocorticoids with or without plasmapheresis. Sever cases of myelitis secondary to systemic lupus erythematosus, cyclophosphamide is used.

Paraneoplastic disorders:

Glucocorticoids and PLEX but long-term remission is based on therapy directed at th underlying malignancy, along with immunotherapy.

TM due to infections:

Treat the underlying infection with suitable agents plus steroids. E.g viral conditions treated wit antivirals and steroids.

Rehabilitation:

Physical and occupational therapy.

AAROM exercise combined with walking exercise. These promote recovery and increas functional abilities.

Bowel dysfunction:

Stool softenrs

Stimlant laxatives

Suppositories

High fiber diet 30g per day

2-3 liter fluid intake

Scanned with CamScanner

Metoclopramide in reserve cases

Bladder dysfunction:

Timed voiding

Clean intermittent catheterization

Condom catheters

Sexual dysfunction:

Prevention of skin breakdown and pressure sores:

Use of air matress and posture position change every 2 hours.

Pain:

Neuropathic pain treated with pregabalin, sertraline, gabapentin.

Muscle pain treated with acetaminophen, ibuprofen, and naproxen sodium.

Psychosocial issues:

Regular counseling and use of antidepressant like sertraline.

Scanned with CamScanner

CIDP

P/C

Lower limb weakness – months or
Weakness of both limbs --- months

HOPI (ODPARA-V)

Same as for Paraparesis but mentioned months instead of days (GBS) , progressively worsening and associated with numbness in glove and stocking distribution and relapse and remitting in nature .there is no associated features of higher mental functions and brainstems (swallowing difficulty , nasal regurgitation etc) .

Imp DDs of CIDP

- DM
- Alcohol induced polyneuropathy
- Syphilis
- HIV induced polyneuropathy
- SCID (↓vit B12)
- Cervical myelopathy
- HSMN
- Paraneoplastic polyneuropathy
- Vasculitis
- AMSAN variant of GBS → in case , duration is short
- Drug induced polyneuropathy (chemo, vincristine, isoniazid and metronidazole)
- CKD
- MUGS→ associated with neuropathy in few cases

Relevant

ITP and FAM-HUGS –FOSS-TV

Examination

Standard neurological examination (always look for imp negative signs of DDs (Uremia, DM, RA, vasculitis this will further narrow the differentials)

Scanned with CamScanner

Chronic Inflammatory Demyelinating Polyneuropathy or Polyradiculopathy (CIDP):

Acquired autoimmune demyelinating condition that affects myelin sheath of peripheral nerves and nerves roots characterized by symmetrical progressive weakness of muscles (proximal and distal) or may have remitting relapsing pattern of disease.

53 years old clerk diabetic from past 11 years began experiencing the following set of symptoms about 6 months ago. Initially, he noticed a tingling sensation in his feet that progressively spread to his legs. Over the next few months, the tingling became persistent and was accompanied by numbness in his lower limbs, particularly at night. He started experiencing muscle weakness, making it difficult for him to climb stairs or stand for long periods. Later, he fined it challenging to get up from chair, open door and hold on objects in hands for longer duration. He also reported strange feeling of heaviness in his legs. On examination, mild muscle atrophy was noted in all limbs tone was slightly decreased, reflexes particularly in his ankles seemed slower than usual. Sensations were reduced in glove and stocking distribution proprioception and vibration sense was more impaired than pain and temperature distally than proximally.

DIFFERENTIAL DIAGNOSIS:

- AIDP (variant of GBS) symptoms progression till 4 weeks
- SIDP. Symptoms progression duration from 4-8 weeks while CIDP symptoms or episodic relapses occur beyond 8 weeks
- CANOMAD (chronic ataxic neuropathy with opthalmoplegia, IgM paraprotein, cold agglutinins, and disialosyl antibodies)
- Multifocal motor neuropathy (MMN)
- POEMS
- Drug induced neuropathy e.g Alpha inhibitors
- Charcot Marrie tooth disease
- Hereditary neuropathy

Association with other Diseases:

- Lyme disease
- Hepatitis B or C
- HIV infection
- Systemic lupus erythematosus
- Thyroid disease, nephrotic syndrome
- Solid organ or bone marrow transplantation
- Inflammatory bowel disease

Variants:

- Multifocal CIDP/ asymmetric
- Focal CIDP

Scanned with CamScanner

- Motor CIDP
- Sensory CIDP
- Mixed CIDP
- Distal CIDP
- Distal and sensory predominant
- Proximal (polyradiculopathy)
- Autonomic predominant CIDP

Investigations:

Nerve Conduction Studies (NCS):

Showed:

- Temporal dispersion and distance-dependent reduction of compound motor action potential (CMAP) amplitude
- Slowed conduction velocities
- Partial conduction block
- Delay or disappearance of F wave
- Prolonged distal motor latencies

Electromyography (EMG):

Revealed evidence of chronic denervation and reinnervation

Lumbar Puncture:

CSF R/E reveals protein levels with a normal cell count (albuminocytologic disassociation), when non- infectious etiology of CIDP.

Imaging:

MRI:

MRI spine done in some cases to rule out other mimics

Nerve biopsy:

In cases where it is difficult to diagnose disease. Biopsy would reveal macrophage associated demyelination and other features.

Nerve ultrasound:

To look for region of involvement; shows nerve hypertrophy

Blood Tests: To rule out other potential causes, look for association with other diseases.

Diagnosis:

Progression over at least two months
Weakness more than sensory symptoms
Symmetric involvement of limbs
Proximal muscles involved along with distal muscles
Widespread reduction or loss of deep tendon reflexes
Increased cerebrospinal fluid (CSF) protein without pleocytosis
NCS evident of a demyelinating neuropathy
Nerve biopsy evident of segmental demyelination with or without inflammation

Scanned with CamScanner

Gait ataxia secondary to large fiber sensory loss. As evident by loss of vibration and position sense more than pain and temperature.

Management:

Goal of Treatment:

To minimize further attacks and minimize disability

Intravenous immunoglobulin:

Rapid response:

Initial dose regimen: 2g/kg for 5 days.

Infusion of IVIG (1 g/kg) every three weeks for next 2 - 3 months after the initial treatment before determining efficacy

Caution:

(IgA) deficient patients should not be treated with intravenous immunoglobulin since it can lead to anaphylaxis.

IVIG should be used cautiously in patients with severe kidney disease.

Plasma exchange:

Same efficacy as IVIGs.

Exchange sessions 4-6 over 8-10 days. These sessions can be repeated to one session per week depending upon patient disability.

Steroids:

Insidious:

When symptoms are not progressing at a greater rate glucocorticoids are given to help achieve remission.

IV pulse-dose glucocorticoids:

Initial dose of IV methylprednisolone (1000 mg/day) for three days followed by 1000 mg one day a week for four weeks,

Oral pulsed steroids:

Dexamethasone:

40 mg for four consecutive days once a month

Or

Prednisone 600 mg once a week

In patients who respond to therapy, we taper either the dose or frequency once improvement or clinical stabilization occurs.

A glucocorticoid course of up to 8 weeks may be required to decide whether there is a treatment response or not.

Maintenance Therapy:

IVIG:

Dose: 1g/kg; if symptoms Worsen 2g/kg

Every two to 3 weeks after initial therapy.

Scanned with CamScanner

Subcutaneous immune globulin (SCIG) therapy may be used as maintenance therapy for patients with CIDP who respond to IVIG treatment.
Then taper off IVIG dose to 0.4g/kg and frequency should be adjusted so that the patient does not deteriorate between doses.

Glucocorticoids:
Start prednisone at 1 to 1.5 mg/kg daily (usually around 50 to 80 mg daily; no more than 100 mg).

Refractory Disease:

For patients with severe CIDP (eg, unstable active disease with a progressive or relapsing course) who are refractory to treatment of (IVIG), steroids, and plasma exchange, alternative immunomodulatory agents include;

- Cyclosporine
- Methotrexate
- Rituximab
- Azathioprine
- Mycophenolate
- Cyclophosphamide

The treatment should be continued until improvement is complete and patients have stabilized (with possible residual deficits). At that point, the treatment either can be tapered or stopped depending upon patient condition. However, clinical surveillance should be continued for years.

Autologous hematopoietic stem cell transplantation:
When every treatment is failed

Physiotherapy:
Crucial along medication therapy

Scanned with CamScanner

MYASTHENIA GRAVIS

Patient of Myasthenia Gravis may present with either muscle weakness, dropping of the eyelid and or double vision .We will discuss each approach briefly

P/C

Muscle weakness

Patient presented with a complaint of muscle weakness that is gradual in onset, progressive and generalized in nature and 3 months in duration .patient describes weakness as feeling of decreased muscle strength and difficulty in carrying out daily life activities like walking up stair, combing hair and household chores. Weakness is more at the end of the day and fluctuating that is worsen with exertion and improve with rest .it is associated sometime with drooping of the eyelid /double vision at the evening and difficulty in swallowing .However , there is no HX of nasal regurgitation of food

DDs of muscle weakness

- Polymyositis → non flucating and associated with pain in the muscle and pain on touching the muscles
- Dermatomyositis→ Hx of rash on the knuckles and eyelids
- Inclusion body myositis→ if age > 50 years
- Hypothyroidism
- Hyperthyroidism
- Addison
- Cushing syndrome
- Drug induced myopathy→ steroid(khakeemi medicine) and statin
- Hypo/hyperkalemic periodic paralysis
- Myotonic dystrophy
- Muscular dystrophies (Duchene ,Becker ,FSHD etc) → family HX of muscle weakness
- Myasthenia Gravis
- Botulism
- Organophosphate poisoning
- Lambert –Eaton syndrome
- Polyneuropathies
- MS
- SOL
- Stroke /TIA
- MND
- Lead poisoning
- Todd's paralysis

P/C

Scanned with CamScanner

Drooping of the eyelid (ptosis)

Patient presented with drooping of the eyelid that is gradual in onset, one month in duration involving one one /both eyes. The patient describes his symptoms as inability to open/blink the eyes properly. According to the patient ,it is fluctuating in nature aggravated by activity that is more in the evening and relived by rest /cold water , however , it reoccur after some activity .it is associated with double vision /muscle weakness /difficulty in swallowing and change in the quality of voice.

DDs

- **Local pathology** (trauma , surgery , pain and redness)
- **DM**
- **Horner syndrome** →HX of loss of sweat in one side of the face and drooping of the eyelid
- **MS**→ HX of blurring of vision and or body weakness that is resolved spontaneously
- **Cluster headache** →Hx of unilateral headache associated with drooping of the eyelid and nasal congestion
- **Congenital** →HX of drooping of the eyelids since birth
- **Botulism** → HX of cane ingestion followed by drooping of the eyelids , difficulty in swallowing and speaking
- **Miller Fisc**→ HX of drooping of the eyes , descending weakness and dizziness
- **Snake bite**
- **Muscular d trophy** → HX of muscular disorder in the family
- **Drugs** → steroids and Hakeemi medication

P/C **Double vision**

Patient presented with double vision that is gradual in onset, episodic in nature and 2 weeks in duration. The patient describe his symptoms as viewing of 2 images as side by side or one at top of the other or at angle of each other .However , distance b/ w the images remain the same in all direction . Double vision is fluctuating in nature present in both near as well as distant gaze .it is aggravated by activity relived by closure of the eyes and recur after some time and also occur on induced fatigability .there is associated HX of difficulty in neck holding, muscle weakness and difficulty in swallowing .

DDs

- **Cavernous sinus thrombosis** →redness of the eyes , facial pain and fever
- **Orbital apex syndrome** (2 orbital fracture ,SOL and cellulitis → HX of double vision associated with decreased visual acuity
- **CNS Pathology (stroke ,SOL, infection)**
- **MS**
- **DM**
- **Graves' disease**
- **Miller Fischer**
- **Botulism**

Scanned with CamScanner

- **Wernickes encephalopathy** →HX of chronic alcoholism and or malnutrition
- **Giant cell arteritis**
- **Benign intracranial hypertension** →Headache that is worse in the morning and aggravated by coughing and sneezing
- **Metastasis**
- **Infection (TB and HIV)**

While DDs of monocular diplopia are

- Cataract
- Corneal disease
- Lens dislocation
- Refractive error
- Macular disease

Now relevant ITP and

PAM-HUGS-FOSS-TV-F

Examination scheme

Vitals

GPE → thymectomy scar, evidence of other autoimmune disorders like RA, SLE, vitiligo

- Jaw supporting sign
- Cushingoid appearance may be present (due to steroid)
- Face and eyes (ptosis which may be unilateral or bilateral with frontalis over activity but normal pupil size)
- Speech may have a nasal twang (ask the patient to count to 50 and see voice may deteriorated)

Eyes

- Fatigability(check extra ocular movement for diplopia and variable squint)
- Peep sign
- Diplopia

Check power in eye muscle, facial muscles, and jaw muscles especially jaw closing .the weakness may be generalized and may affect the limb muscles esp proximal muscles, diaphragm and neck extensor

Could you please puff out your cheeks?

Could you please smile (myasthenia snarl)

Now can you please open your mouth and say ah (movement of uvula)

Power in neck muscles and arms, including fatiguability

Gait (waddling)

Examination of the upper limbs, there is evidence of

- Proximal weakness and fatiguability
- Deep tendon reflexes and sensations are normal
- Gait is normal (waddling)

Scanned with CamScanner

VIVA OF MYASTHENIA GRAVIS

Myasthenia Gravis:

Is an autoimmune neuromuscular disorder characterized by fluctuating motor weakness involving ocular, bulbar, limb, and/or respiratory muscles.

45 years old male patient presented with complaints of generalized weakness and fatigue. He was having difficulty walking also it was difficulty to get up from sitting position. He also complaint of bilateral diplopia. Now he has got difficulty speaking. Past history significant for type 1 diabetes for which he is administering inj humelin since 20 years. On examination; bilateral ptosis was present. Lid curtain, peek sign was positive. Sustained up gaze resulted in worsening of diplopia. On ice pack test diplopia got improved. He was having restricted eye movements as well. Cough reflex was weak. Single breath count was upto 11. Power was 4/5 all limbs. Neck extension and flexion was weak. Patient was asked to lift right arm 20 times however lifting for 7 times only resulted in fatigue. Tone and reflexes: normal. Babinski: absent.

Differential Diagnosis:

- Lambert-Eaton myasthenic syndrome
- Botulism
- motor neuron disease
- Steroid induced myopathy
- Brainstem and cranial nerve lesions
- thyroid ophthalmopathy
- oculopharyngeal muscular dystrophy
- chronic external opthalmoplegia
- Malignant or obstructive nasal or pharyngeal pathology
- Paraspinous myopathy
- Inflammatory myopathy
- CIDP

Clinical suspicion of MG:

After surgical procedure:

Neuromuscular weakness is suspected in patients who do not improve as expected with neuromuscular blockade reversal following general anesthesia. Neuromuscular respiratory failure may be thee first sign of MG.

Pharmacological testing:

Edrophonium tensilon test:

This test is obsolete now however administration of Edrophonium results in improvement in muscle power as it is an acetylcholine esterase inhibitor with onset of action in 30-45 seconds.

Scanned with CamScanner

Investigations:

Serological Testing:

The diagnosis may be confirmed by the presence of autoantibodies against

1st line antibody testing: acetylcholine receptor (AChR) antibodies. High titers are more specific for diagnosis of MG than low titers.
Usually positive in 85 percent of cases.
Thymic hyperplasia and thymoma present with AChR antibodies positive MG.
2nd line antibody testing: muscle-specific tyrosine kinase (MuSK) antibodies:
These are common in cases upto 8 percent; not related to thymoma. It is detected mostly in oculobulbar form of MG.
Low-density lipoprotein receptor-related protein 4 (LRP4):
Patient with these antibodies are labeled as double seronegative MG.
Not associated with thymoma. Present in 1 percent of cases.

Seropositive MG

Patients with AChR, MuSK, or LRP4 antibodies

Seronegative MG:

Ppatients who do not have any of these autoantibodies and are diagnosed by electro diagnostic testing

Electro Diagnostic Testing:

RNS:

Repeated stimulation of a motor nerve results in progressive reduction in the amplitude of the compound muscle action potential (CMAP) showing neuromuscular impairment. It is considered positive if there is decremental response more than 10 percent.

Post Exercise Exhaustion:

Patient is asked to do the task for 30-60 seconds at specific muscle and is repeated at 1 minute, 3 minutes time and assess if there is decremental response post activity.

EMG:

Usually done in different muscles to check impairment of motor nerve, muscle, or neuromuscular junction to exclude other pathologies

Single Fiber EMG: Most sensitive diagnostic test for MG. Increased jitter is the hallmark feature.
Allows simultaneous recording of the action potentials of two muscle fibers innervated by the same motor axon. The variability in time of the second action potential relative to the first is called "jitter." Increased jitter occurs when neuromuseular transmission is impaired.

MRI BRAIN:

To rule out brainstem stroke

CSF / RE:

Scanned with CamScanner

Rule out brain infection.

CT / Ultrasound Orbits:

To look for orbital mass or tumor

Ct/MRI Mediastinum:

For thymoma

Autoimmune Profile:

Workup should be done for associated diseases like autoimmune thyroiditis, rheumatoid arthritis, SLE.

Management of MG:

The goals of therapy in MG are to render patients minimally symptomatic or better while minimizing side effects from medications.

Pyridostigmine: anticholinesterases inhibitor

Dose:

Initial 30mg 2-3 times with meals for 3 -4 days for assessing cholinergic effects.

Max dose: 1.5g/day.

NOTE: For those with excessive cholinergic side effects we add an anticholinergic agent with each Pyridostigmine.

- Glycopyrrolate 1 mg PO
- Propantheline 15 mg PO
- Hyoscyamine sulfate 0.125 mg PO

Prominent diarrhea can be reduced by the addition of loperamide or diphenoxylate hydrochloride-atropine sulfate (Lomotil).

Pparadoxical weakening with anticholinesterase medications is called **"cholinergic crisis."** However, cholinergic crisis is rarely if ever seen with dose limitation of Pyridostigmine to ≤120 mg every three hours.

Glucocorticoids:

Pprednisone at 20 mg daily and then increase by 5 mg every three to five days to a usual target dose of 60 mg per day (or 1 mg/kg per day, maximum 80 mg daily).

Given to patient whose disease is control and is not progressing.

Prevention of osteoporosis:

Calcium (1500 mg per day) and vitamin D (400 to 800 international units per day) supplementation should be used to reduce bone mineral loss.

Steroid Sparing Agents:

- Azathioprine
- Mycophenolate
- Rituximab
- Cyclophosphamide

Scanned with CamScanner

- Tacrolimus
- Cyclosporine

Antibody-Based Biologic Therapies (Recent Advances):

- **Efgartigimod alfa –fcab** (target the FC receptor and resulting in reduction of IgG and indicated in AChR antibody positive patient)
  - Dose → weight < 120 kg : 10mg kg IV /week for 4 weeks and if > 120 kg than 1200mg IV weekly for 4 weeks
- **Rozanolixizumab**(monoclonal antibody with same MOA)
  - < 50 kg → 420 mg SC infusion weekly for 6 weeks
  - 50-10 kg → 560 mg SC infusion weekly for 6 weeks
  - > 100 kg → 840 mg SC infusion weekly for 6 weeks
- **Ravulizumab** (monoclonal antibody that is terminal complement inhibitor) prophylaxis is for meningococcal encephalitis should be done 2 weeks before administration.
- **Zilucoplan(** bind to complement protein C5 and preventing the generation of the terminal complement complex , C5b-9)
  It also needs meningococcal infection prophylaxis.
  - < 56 kg → 16.6 mg SC /day
  - 56-77 kg → 23 mg SC/day
  - ≥ 77 kg → 32.4 mg SC /day

Myasthenic Crisis: is a life-threatening exacerbation of myasthenia gravis that is defined as worsening of myasthenic weakness requiring intubation or non-invasive ventilation.

Risk factors:

- Greater disease severity at diagnosis
- Presence of thymoma
- Association with MUSK antibodies

Precipitants:

- Infections
- Drugs
- Surgery
- Pregnancy
- Childbirth
- Tappering medications

Management: Admit to intensive care unit *ICU*.

Assessment of respiratory muscle strength:

Low baseline vital capacity (VC) that is <30 mL/kg of body weight shows impending respiratory failure even if patient is not distressed. VC falls below 15 to 20 mL/kg needs elective intubation. Symptoms of failure include weak cough reflex, hypophonia, shortness of breath.

Intubation:

If clinical evaluation or tests of respiratory muscle strength suggest impending respiratory failure; temporarily stop anticholinesterase medications for intubated patient.

Rescue therapy:

Scanned with CamScanner

Begin rapid therapy with plasma exchange 4-6 sessions in 8-10 days.

Or

Intravenous immune globulin (IVIG). The total dose of IVIG is 2 g/kg, usually over two to five days (eg. 400 mg/kg per day over five days).

Immunomodulating therapy:

Begin with high-dose glucocorticoids; The quick onset of action of rapid therapies helps to prevent the transient worsening that would otherwise occur due to starting .steroids Consider azathioprine or mycophenolate mofetil if glucocorticoids are contraindicated .

Weaning from mechanical ventilation:

When respiratory muscle strength is improving after resuming anticholinesterase medications and treatment with plasma exchange or immunoglobulin

Drugs to Avoid In Myasthenia Gravis:

- Neuromuscular blocking agents:

(Rocuronium, vecuronium)

Antibiotics:

- Aminoglycosides:

(Amikacin, gentamicin, neomycin, tobramycin)

- Fluoroquinolones:

(Ciprofloxacin, levofloxacin, moxifloxacin, ofloxacin)

- Macrolides

(Azithromycin, clarithromycin, erythromycin)

- Beta-blockers

(Atenolol, labetalol, metoprolol, propranolol)

- Others:
  - Botulinum toxin
  - Procainamide
  - Quinidine
  - Chloroquine
  - Deferoxamine
  - Iodinated contrast
  - Statins
  - HCQ
  - Calcium channel blockers
  - Phenytoin
  - Gabapentin
  - Lithium
  - Phenothiazine

Vaccination:

Annual seasonal influenza vaccination PLUS pneumococcal for all individuals receiving immunosuppressive therapy and for those with neurologic conditions .

Reader is advice to also read MG in neurology short cases section

Scanned with CamScanner

APPROACH TO TREMORS (Due to Parkinsonism)

P/C

Worsening of tremors

HOPI (ODPARAV)

My patient presented with worsening of tremors (abnormal involuntary shaking of hands) that is gradual in onset, progressive in nature and .... Duration .According to the patient, tremors were initially involved one hand followed by the other hand. Tremors are present at rest as well as during activities. There is no involvement of tongue, head and lower limbs. Tremors are aggravated by stress activities and relived by sleep and with medication. Additionally, tremors are associated with stiffness of the joints, difficulty in walking (initiating walking, turning back and slowness of movement) changing position in the bed and difficulty carrying out daily activities like shaving, writing and dressing.

DDs of tremors

- Essential Tremors → there is no family HX of tremors of hands and head
- Thyrotoxicosis → there is no HX of heat intolerance and palpitation
- Anxiety →
- Pheochromocytoma → no HX of episodic sweating , headache associated tremors
- Hypoglycaemia → no HX of low blood glucose
- Alcohol withdrawal→ No HX of chronic alcoholism
- Hepatic encephalopathy→ no HX of liver disease , black tarry in the stool
- Wilson disease → no family HX of liver disease in the family
- Parkinson disease (long case)
- Multi –System atrophy (MSA)→there is HX /no HX of urinary retention , loss of sweating and dizziness on standing (postural hypotension) associated with tremors
- Supra nuclear palsy (PSP)→ HX of impairment of vertical gaze
- Lewes body dementia → no HX of visual hallucination associated with tremors
- Drug induced tremors (LBD)→ no HX of drug intake like thyroxine , velproic acid and recreational drugs
- Dystonia's

CARE of Parkinsonism

VODDKAS

- Vertical gaze palsy → PSP
- Orthostatic hypotension →MSA
- Dementia → with visual hallucination →LBD
- Drugs →dopamine antagonist like haloperidol and metoclopramide
- KF-rings → Wilson disease
- Apraxia and urinary incontinence → NPH
- Stroke → HX of weakness of any part of the body
- Idiopathic (most common cause)
- Toxins→ no HX of exposure to CO , manganese and MPTP
- Post-encephalitis → there is no HX of altered behaviour ,fits and high grade fever
- Dementia Pugilistica→ there is no HX of recurrent fall or punch to head
- No HX of loss of smell ,tendency to falls ,drooling of saliva , reduced blinking of eyes

Scanned with CamScanner

Now relevant ITP and
PAM-HUGS-FOSS-TV-F

Examination

Assess speech (low volume, monotonous)

General inspection (look at the face carefully)

- Expression (mask like)
- Drooling of saliva
- Infrequent blinking

Examination of upper limbs like hands and arms

Inspection (ask the patient to keep the hands in semi-prone position)

- Resting tremors
- Bradykinesia

Motor system and synkinesis while cheeking tone

- Look for Cortico-basal degeneration (draw something on hand like write some letter and ask to explain)
- Finger nose test
- Button and unbutton or pick up a coin
- Writing (micrographia)

Face and eyes

- blephroclonus

Eye movement (nystagmus and upward gaze palsy)

Gait

- Freezing
- Posture
- Arm swinging
- Turning back

Also

- MMSE
- Check the posture drop.

Scanned with CamScanner

VIVA PARKINSONISM:

PARKINSONISM:

Set of clinical syndrome presenting with any combination of bradykinesia, rest tremor, rigidity, and postural instability.Progressive neurodegenerative disorder previously called as shaking palsy characterized by motor disorders with the features of bradykinesia, rigidity, and tremor with many other non -motor symptoms.

54 years old school teacher with masked facial features who has Parkinson from past 3 years and is on medication have trouble getting out of bed, She notices that her movements are a bit slower than usual, and her hands tremble slightly and is difficult for her to button up her shirt , taking money from purse or to hold objects. She often has some difficulty swallowing chewing food as well. She took her morning medicationn levodopa/carbidopa that helps manage her symptoms. She follows a stretching routine recommended by her physical therapist to ease her stiffness. She has a short shuffled gait. Her tremors are more noticeable in resting condition.

DDs

- Parkinson disease
- Essential tremor
- Dementia with Lewy bodies
- Multiple system atrophy
- Corticobasal degeneration
- Progressive supranuclear palsy
- Idiopathic and familial basal ganglia calcification
- Huntington disease
- Spinocerebellar ataxia
- Front temporal dementia with parkinsonism

Secondary Parkinsonism:

- **Drug-induced:**
- Antipsychotic agents
- Metoclopramide
- Prochlorperazine
- Tetrabenazine
- Sodium valproate

Toxic:

- Carbon disulphide
- Carbon monoxide
- Cyanide
- MPTP
- Manganese
- Organic solvents

Vascular:

Scanned with CamScanner

- Vascular Parkinsonism
- Vascular dementia

Structural:

- Normal pressure hydrocephalus
- Chronic subdural hematoma
- Tumors involving striatonigral circuits
- Head trauma

Genetic:

- Wilson disease
- Neurodegeneration with iron accumulation
- Neuroacanthocytosis

Infectious:

- Encephalitis lethargica
- HIV/AIDS
- Neurosyphilis
- Prion disease
- Progressive multifocal leukoencephalopathy
- Ttoxoplasmosis

Functional Parkinsonism: Functional tremor without evidence of bradykinesia or cogwheel rigidity, the other cardinal signs of true Parkinsonism

FEATURES (examination and HX points)

MOTOR:

Tremor ... more marked in resting condition. Half of patients have a feeling a sensation of internal tremulousness in the limbs or body. On distraction tremors increases as well.

Bradykinesia: decrease amplitude of movement. On examination arm swing is less on the effected side and gait revealed shorter steps. Carefully observe speed, amplitude, and rhythm of finger tapping, hand opening-closing, pronation-supination hand movements, and heel or toe tapping.

Rigidity: increased resistance to passive movement about a joint Rigidity is tested by passively by moving the limbs or asking the patient to through imaginary ball through other contralateral limb so rigidity is increased in the other limb.

- **Others:**
- Postural hypotension
- Cognitive dysfunction and dementia
- Psychotic symptoms (hallucinations and delusions)
- Mood disorders including depression, anxiety, and apathy/abulia
- Sleep disturbances
- Fatigue
- Autonomic dysfunction
- Olfactory dysfunction

Scanned with CamScanner

- Gastrointestinal dysfunction
- Pain and sensory disturbances
- Blurred vision
- Impaired contrast sensitivity
- Speech impairment,
- Dysphagia is due to bradykinesia of the pharyngeal muscles which can lead to pooling of saliva in the mouth and drooling.
- Sialorrhea
- Kyphosis
- Scoliosis
- Myoclonus
- Dermatological manifestations (sebborhic dermatitis, melanoma)

Clinical Subtypes On Based Of Symptoms:

One of the symptoms is predominant.

- Tremor-dominant
- Akinetic-rigid
- Postural instability and gait difficulty

Management:

Treatment should be when motor symptoms are affecting function and quality of life.

Levodopa: mostly patients on monotherapy.

Carbidopa-levodopa (Sinemet) 25 mg/100 mg, initially started half tab TDS with meals. Immediate release is the preferred initial formulation. Tremor predominant tremor levopda needs higher doses of levodopa.

Dose is titrated upto 2 tablets depending on symptomology.

Side effects:

Nausea ,Somnolence, dizziness , headache ,confusion ,Hallucinations ,delusions , agitation ,Psychosis ,orthostatic hypotension ,Decrease vit B12 Level ,increase risk of fractures ,Increase risk of

Motor complications of LEVODOPA:

Motor fluctuations ("wearing off")... treatment strategy:

Closer spacing of doses to bridge the gaps and adding drugs that extends the benefit of levodopa.

Failed doses

Involuntary movements (dyskinesia)

Abnormal cramps

Postures of the extremities and trunk (dystonia)

Note

Levodopa should **not** be stopped abruptly in patients with PD, because sudden withdrawal has been associated (rarely) with a syndrome resembling neuroleptic malignant syndrome or Akinetic crisis.

Scanned with CamScanner

Non- ergot dopamine agonist:

Pramipaxole, rotigotine, ropirinole

Intermediate potency for managing motor symptoms can be used an alternative to levodopa.

Avoid in patients older than 50 years due to cognitive impairment.

Oral: Pramipaxole, ropirinole 2-3 times per day.

Transdermal: rotigotine once a day

Rescue therapy: apomorphine subcut or sublingual in sudden akinetic episode.

Warning: should not be stopped at once due to akinetic crisis and neuroepileptic malignant syndrome.

Contraindicated in breast feeding

MAO Inhibitors:

In patients of any age preferring once-daily medication; a reasonable alternative to levodopa as first-line therapy

Selegiline: 5mg oral BD

Others:

Rasagiline and safinamide

Amantadine:

Effective in tremor predominant disease with or without with levodopa

Dose: 100-200mg BD

Avoid at night as it causes insomnia

Anticholinergic

- Centrally acting anticholinergic
- Trihexyphenidyl
- Benztropine
- Biperiden
- Orphenadrine
- Procyclidine

Neurointerventional Therapy:

- Deep brain stimulation
- Focused ultrasound therapy
- Continuous carbidopa/levodopa intestinal gel infusion
- Continuous subcut apomorphine

Others: Monotherapy:

Mild symptoms preference for once-daily medication→ **Monoamine oxidase inhibitors type B**

Younger patients at high risk for dyskinesia→ **Non -ergot dopamine agonists**

Patients with tremor-predominant disease: → **Amantadine**

Also read PK in neurology short cases

Scanned with CamScanner

APPROACH TO ALTERED SENSORIUM (Due to seizure)

HOPI (ODPARAV)

HX of complete loss of consciousness /drowsiness, gradual/onset that last for certain duration .any involuntary body movements and stiffness of body .HX of aggression ,irritability and any mood and memory impairment . Tongue bite and urinary incontinence.

DDs

Same as discussed in hypertension section and additional DDs are as follow

- Seizure
- Brain abscess
- HIV/TBM and toxoplasmosis
- Eclampsia
- Conversion disorder
- Arrhythmias
- Autoimmune disorder like lupus cerebritis
- Neurosyphilis
- Drugs (recreational) and alcohol withdrawal

Complications

Fracture of bones, aspiration pneumonia, AKI due to muscles injury and complication due to drugs like weight gain and gums hypertrophy

ITP and PAM-HUGS-FOSS-TV

Examination

Always look for possible underlying pathology (imp signs)

Scanned with CamScanner

VIVA

EPILEPSY: defined as occurrence of two or more than two seizures occurring 24 hours apart.

22 years old college student presented in a state of altered sensorium with complaints of sudden onset of generalized tonic colonic fits for 3 to 4 minutes with urinary incontinence and frothing from mouth. Her classmates gave history of one such episode few months back .Her family history was also positive for epilepsy. She stayed unconscious for 10 minutes after this period (postictal state).

Examination was unremarkable except power of 3/5 in left arm (TODDS PARALYSIS) . She was vitally stable.

Investigations:

Aim to diagnose and exclude DDs

To make plan of management

- CBC, RFT,LFT ,S/E
- SERUM CALCIUM (total and ionized)
- Serum MAGNESIUM
- RBS
- Urine and blood toxicology screening
- CSF STUDIES in case of suspected infections
- Pregnancy test
- EEG (however normal EEG never rules out epilepsy)
- MRI BRAIN (rule out structural disease
- Genetic studies in some cases.

Treatment of Epilepsy in Adults:

When To Start Treatment:

Case of first unprovoked seizure:

- Depends on risk vs benefit formula (potential benefits and side effects of anti -epileptic medications)
- Risk of recurrent attacks
- Choice of patient and family
- Essential to start treatment in cases of trauma , stroke and brain tumor
- Abnormal findings on CT, MRI AND EEG
- Abnormal neurological findings
- First nocturnal seizure (that occurs while sleeping)

Two or more seizures:

These are at high risk of further attacks and anti-epileptic medications must be started in these cases. Previous researches have proven that earlier start of medication improves quality of life of patient and decrease recurrence of further attacks.

Scanned with CamScanner

Choice of Anti -Epileptic Medication:

- Depends on type of seizure (focal, generalized, absence)
- Age
- Gender
- Financial status
- Side effects
- Relative co morbid conditions (mainly liver and kidney diseases)
- Drug interactions

Enzyme inducer antiepileptic medication like phenytoin, carbamazepine, oxcarbazepine, and phenobarbital interact with warfarin, OCPS, some antcancer drugs and reduce their efficacy.
Single drug is started and its efficacy and side effects are monitored. Basic formula is to titrate up 1st medication and if fits still not controlled add second antiepileptic drug accordingly.

Drugs According To Type of Seizure:

For both generalized and focal (broad spectrum)	Focal mainly ; but also work in generalized convulsive disorder that evolves from focal seizures	Absence
Sodium valproate, Levitriacetam ,topiramate, brivaracetam Zonisamide, Rufinamide, lamotrigine,	Gabapentin,lacosamide Phenytoin,primidone,vigabatrin , Strirpentol,carbamezapine,oxcarbazepine, Eslicarbazepine,	Ethosuximide
CAUTION: Lamotrigine precipitate or exaggerates myoclonic fits Sodium valproate exacerbates fits in mitochondrial diseases.		

Scanned with CamScanner

SIDE EFFECTS OF ANTIEPILEPTIC MEDICATIONS:

NAME OF DRUG	COMMON	Serious side effects
SODIUM VALPROATE	Weight gain, hairloss, tremor,	Steven Johnson syndrome (SJS) / toxic epidermal necrolysis (TEN). Liver failure, PCOS, aplastic anemia, aganulocystosis , pancreatitis, hypogammaglobinemia, teratogenic
LEVITRIACETAM	Fatigue,	Angioedema,pancytopenia,aggressive behaviour, psychosis, abnormal movements, forgetfulness, SJS, Nephrotoxicity , TEN
LAMOTRIGINE	Rash	Arrhythmia, DRESS Syndrome, SJS, TEN, aseptic meningitis,hypogammaglobinemia
LACOSAMIDE	Fatigue	Conduction heart blocks, neutropenia, hypersensitivity reaction, depression, hyperhidrosis,
PHENOBARBITAL	Rash, tolerance dependence	Hepatic failure , dupuytren contractures, regional pain syndrome, Agranulocytosis, dermatitis, thinking abnormality, hallucinations, decrease libido, vitamin D Deficiency
PHENYTOIN	Gingival hyperplasia, rash	Apalstic anemia, SJS, TEN, neuropathy, pseudo lymphoma, liver failure, drug induced lupus , hirsutism , teratogenic
TOPIRAMATE	Weight loss, fatigue, numbness	Hyperthermia due to oligohydrosis, eye problems (myopia & glaucoma) nephrolithiasis. (Avoid ketogenic diet as it increases ketosis and risk of kidney stones.)
ETHOSUXIMIDE	GI disturbances	Exfoliative dermatitis, SJS, eosinophilia, .

Note: almost all antepileptics have side effects of nausea, vomiting dizziness, somnolence, altered sleep cycle, increase suicidal tendency, and mood disorders.

Scanned with CamScanner

Epilepsy in Females of Child Bearing Age:

Preconception Era:
Education and Counseling:
Must be educated on the following:

- Folic acid supplementation
- Potential hazards and side effects of medications
- Risks in case of unplanned pregnancy
- Optimization of antiepileptic medications in pregnancy
- Use of appropriate contraceptives

Contraception:

Best methods include barrier methods, use of intrauterine device or intramuscular depot.
Use of hormonal medications is responsible for unplanned pregnancy due to hepatic enzyme induction phenomenon associated with these drugs.

Non-Inducers Antiepileptic's are:

- Ethosuximide
- Lacosamide
- Pregabalin
- Zonisamide
- Gabapentin
- Levitriacetam
- Sodium valproate

Selection of Antisezure Medication:

- Safe options include:
- Levitriacetam
- Lamotrigine
- Carbamazepine

Greatest risk of neural tube defects occurs with valproate and topiramate

Folic Acid Supplementation:

Lowers risk of neural tube defects

Management during Pregnancy:

Dose Adjustment and Modification of Antiepileptic Drugs:

Carbamazepine:

Best for focal onset seizures
Also associated with low teratogenic risks and normal cognition of baby

Scanned with CamScanner

Lamotrigine:

Although safe but therapeutic dose cannot be started at once in start of pregnancy due to risk of rash. Its level decreases in blood in all trimesters due to increase clearance .So, it is advised to monitor drug levels that the levels do not fall more than 65 percent of prepregnancy period to avoid seizures.

- Lacosamide:
- Phenobarbital:
- Levitriacetam:

Good safety profile; also broad spectrum covering multiple seizure types.

Note:

Highly protein bound drugs phenytoin, carbamazepine, sodium valproate and phenobarbital concentrations don't change in blood in pregnancy.

It is advisable to titrate up dosage after 1st trimester where:

Metabolism of drugs is increased. Example includes lamotrigine, Levitriacetam, oxcarbazepine.

Patient was on lowest dosage at prepregnancy stage as thresh of seizures increases in pregnancy.

Focal fit changed to generalized tonic clonic

Change of Medications during Pregnancy:

Medication change is not advisable as alteration and transition of medication increase the risk for seizures. However, in cases where female is on multiple antiepileptic with good seizure control, one drug or more may be removed if there is lower risk of seizure recurrence ; to lower the risks of neurodevelopmental to fetus.

Continue Folic Acid:

Dose :0.8 mg to 1mg pre pregnancy and throughout pregnancy ; however woman taking valproate and carbamazepine 2 mg to 4mg per day.

Monitoring Fetal Growth and Screening Malformation:

Anomaly scan: after 18th week for neural tube defects and growth scan between 26 to 30th week and 32 to 35th week for fetal well-being.

Management during Labour:

New onset seizures must be excluded for possible eclampsia and dural sinus thrombosis.

Threshold of fits increases in last trimester as well as during delivery.

Should be given epidural anesthesia to cope pain and stress as stress pain and lack of sleep can trigger seizures.

In case of seizure:

IV Lorazepam is the drug of choice. 1mg for non-convulsive while 2mg for GTC.

Magnesium sulphate is not advisable for epilepsy in fits until and unless there is evidence of fit due to eclampsia.

Effect of Medication on Fetus:

Antiseizure medications can cause decreased responsiveness in fetus and cause fetal abstinence syndrome in first few days of life specially with drugs like primdone, phenobarbital

Management during Postpartum Period:

Scanned with CamScanner

Rest and Avoidance of Sleep Deprivation:

It is advisable to give appropriate rest and sleep to avoid triggering seizures.

Postpartum Dose Adjustment of Medications: Levitriacetam and other like gabapentin, topiramate, and velproic acid etc dose is tapered off over 3 to 4 weeks.

Medications like carbamezapine and others which are metabolized by cytochrome P450 enzymes need to tapered more slowly over 6 weeks.

Lamotrigine dose is tappered off quickly as its rate of clearance decreases abruptly in postpartum.

Breast Feeding:

Mothers are encouraged to breast feed as effects on Antiseizure medications in nursing babies are lacking.

General Safety:

Not advisable to do driving, or take shower behind closed doors or carry baby without a carry cot or a stroller. Attendance must provide assistance to mother in all cases.

Scanned with CamScanner

STATUS EPILEPTICUS

Convulsive state also called status epileptics is defined by seizures that are prolonged mo
5 minutes or immediately recurrent without a return of consciousness.

Algorithm for management:

Follow the protocol.

A: airway (oxygenation, suctioning, lateral decubitus position)

B: breathing

C: circulation

Double IV ACCESS

Monitor vitals: search for reversible causes. Never forget glucose (hypoglycemia causes fi

1st Line Medications: 0- 5 min

Lorazepam 0.1mg/kg. Max dose 4mg. can be repeated once in 4 minute duration.

Or

Midazolam 10mg IM once

2nd Line Medications: 10-15 min

Levitriacetam 60mg/kg IV, max dose 4500 mg

Or

Valproate 40mg/kg IV, max dose 3000 mg

Or Fosphenytoin or phenytoin 20mg/kg IV. Max dose 1500mg

REFRACTORY STATUS EPILEPTICUS:

When seizures are still not controlled despite of using two IV Antiseizure medications and the medication is benzodiazepine.

Advanced airway management is done (assisted ventilation) .

ICU care with continuous EEG monitoring.

Medications which can be used are:

- Propofol: 2-5mg/kg IV then infusion of 2-10mg/kg/hr
- Ketamine: 0.5-3mg/kg IV , then infusion of 0.3-4mg/kg/hr
- Midazolam: 0.2mg/kg IV , then infusion of 0.05-2mg/kg/hr
- Lacosamide: 400mg IV over 15 minutes then 200mg BD
- Phenobarbital: 15-20mg /kg IV at 50-75mg/min

SUPER REFRACTORY STATUS EPILEPTICUS:

Persistence of seizures for 24 hours or more after giving anesthetics (third line medicati

or

Burst of seizures after withdrawal of the anesthetics.

Management:

- Assisted ventilation
- ICU care
- Continuous video EEG Monitoring

Scanned with CamScanner

- Manage with anesthesia with anticonvulsants :
- Wean off from anesthesia in next 24-48 hours. It is important to note to maximize dose of anticonvulsants while tapering off anesthetics.
- If no fits ; observe and shift toward accordingly
- However : in case of recurrence ; following alternatives should be considered
- Immunotherapy
- Electrical and magnetic stimulation therapies
- Magnesium infusion
- Pyridoxine infusion
- Emergent resective epilepsy surgery

STAGES OF STATUS EPILEPTICUS :

- Stage 1: Early Status Epilepticus (first 30 minutes)
- Stage 2: Established Status Epilepticus (30-120 minutes)
- Stage 3: Refractory Status Epilepticus (>120 minutes)
- Stage 4 : Super Refractory Epilepticus (after 24 hours)
- Stage 5: Prolonged Super Refractory Status Epilepticus (that persists atleast for 7 days)

NON CONVULSIVE STATUS EPILEPTICUS:

Definition

Seizure activity without convulsions and without recovery of consciousness between the ongoing seizures, lasting more than 10 minutes duration with EEG showing ictal activity > 12 minutes in an hour.

Diagnosis:

Continuous EEG is sensitive test for diagnosis.

Treatment:

IV antepileptics given and look for significant improvement in the EEG pattern.

Scanned with CamScanner

Demyelinating CNS Disorders:

For detail discussion of MS, see neurology short case section

FEATURE	MULTIPLE SCLEROSIS	NMOSD	MOGAD
Age	Third decade	Fourth decade	Early to Mid 30
Disease course	Relapsing or progressive	Relapsing	Monophasic or relapsing
Common disease features	Myelitis, optic neuritis, brainstem, cerebral episodes; myelopathy for progressive multiple sclerosis	any combination of myelitis, optic neuritis, area postrema syndrome	Initial episode: optic neuritis (with optic disc edema in >85%), ADEM, NMOSD, myelitis, unilateral cortical encephalitis Relapse: optic neuritis
CSF	WBC <50/mm3 × 106/L (lymphocytic) or can be normal; oligoclonal bands in 85%	WBC variable (usually lymphocytic but can be neutrophilic or eosinophilic); oligoclonal bands in 30%	WBC (lymphocytic); oliogoclonal bands in 5 to 20%
Recovery	Good	Often incomplete	Good
MRI brain	Ovoid periventricular (Dawson fingers), Juxtacortical, cortical, infratentorial, peripheral, ring-/open ring-enhancing	Often normal/nonspecific; if present, area postrema, peri- third/fourth ventricle, splenium, diffuse corpus callosum, pencil-thin ependymal or cloud enhancement	ADEM-like fluffy white matter, deep gray matter, diffuse/confluent brainstem including cerebellar peduncles, unilateral cortical swelling, leptomeningeal enhancement
Attack	Mild to moderate	Moderate to severe	Moderate to severe

Scanned with CamScanner

MRI Spine	Multiple lesions; short lesions; periphery of cord (dorsal/lateral column); ring or variable enhancement	Single lesion (longitudinally extensive transverse myelitis 85%; short 15%); central on axial; ring or variable enhancement	Multiple lesions (75% longitudinally extensive transverse myelitis; 25% short); Conus involved; central on axial, often with H-sign; enhancement <50%
MRI EYE	Usually unilateral; enhancement of <50% of nerve affected; middle of optic nerve	Unilateral or bilateral; enhancement of >50% of optic nerve; posterior optic pathway involving chiasm	Unilateral or bilateral; enhancement of >50% of optic nerve; anterior optic pathway (hence optic disc edema common)
Biomarker	None	Aquaporin 4 antibody	MOG antibody
Acute treatment	IV glucocorticoids; plasma exchange (rarely required)	IV glucocorticoids; plasma exchange (often required)	IV glucocorticoids; plasma exchange (sometimes required); IVIG (used in children)
Maintenance treatment	Variety of approved immunomodulatory medications like (Natalizumab, ocrelizumab, ofatumumab, ublituximab, and alemtuzumab) (cladribine),fingolimod)	azathioprine, mycophenolate, rituximab, tocilizumab Others ; eculizumab, inebilizumab, and satralizumab	none needed if monophasic; glucocorticoids-sparing for relapsing disease (azathioprine, IVIG mycophenolate, methotrexate, rituximab)

For discussion on MS, kindly read MS in neurology short section

Scanned with CamScanner

McDonald criteria for MS

Clinical presentation	Additional data needed
≥2 attacks (relapse) ≥2 objective clinical lesion	None (clinical evidence sufficient additional evidence desirable but must be consistent with MS
≥2 attacks 1 objective clinical lesion	Dissemination in space demonstrated by: MRI Or positive CSF and ≥2 MRI lesion consistent with MS Or further clinical lesion involving a different site
1 attacks ≥2 objective clinical lesion	Dissemination in time demonstrated by:MRI Or second attack
1 attack 1 objective clinical lesion (monosymptomatic presentation)	Dissemination in space demonstrated by: MRI Or positive CSF and ≥2 MRI lesion consistent with MS and dissemination in time demonstrated by: RI or second attack
Insidious neurological progression suggestive of MS (primary progressive MS)	Positive CSF and Dissemination in space demonstrated by : MRI evidence of 9 or more T2 brain lesions or 2 or more spinal cord lesions or 4-8 brain and 1 spinal cord lesions or positive VEP with 4-8 MRI lesions or positive VEP with <4 brain lesions plus 1 spinal cord and Dissemination in time demonstrated by : MRI Or continued

Scanned with CamScanner

TUBERCULOUS MENINGITIS:

Inflammation of the meninges of brain or spinal cord due to gram positive rod mycobacterium tuberculosis

25 years old male who presented with complaints of low grade fever with night sweats, three episodes of generalized tonic clonic fits and headache and decrease vision from past 2 weeks. He was experiencing anorexia and weight loss as well. He had history of pulmonary TB 3 years back but he didn't complete the medication course. On examination, neck stiffness was positive. Tone was normal in all limbs. Power 5/5 all limbs with brisk reflexes. Babinski sign positive. Fundaoscopy revealed papilledema (blurred optic disc). Chest auscultation revealed scattered coarse crepts in all zones bilaterally. Rest of the examination was normal. Vitals: BP: 100/60 mmHg, pulse: 105 bpm, temp: 100F.

- **Differential Diagnosis:**
- Fungal meningitis
- Neurosyphilis
- Neuro brucellosis
- CNS Lymphoma
- Encephalitis
- Brain abscess
- Brain tumor
- Typhoid encephalopathy
- Ameobic meningoencephalitis
- Partially treated brain infection
- Brain Mets
- Cerebral malaria
- Metabolic encephalopathy
- Neurosarcoidosis
- HIV induced encephalopathy
- Neoplastic meningitis

Spillage of tubercular bacilli and tubercular protein:

Complications of TBM

The spillage of exudates in subarachnoid space is responsible for complications of TBM due to hypersensitivity response at the level of the base of the brain caused by the tubercular protein. These are;

Formation of hydrocephalus (communicating due to inflammation of basilar cisterns and non-communicating due to exudate spillage around brainstem area or due to obstruction of aquaduct. VP shunting or endoscopic ventriculostomy is done.

Tuberculous vasculitis:

Scanned with CamScanner

Cerebral vessels inflammation leading to occlusion of blood supply causing infraction and damage of the brain.

Cranial nerve palsies and periventricular infract:

Exudate encase along cranial nerves and periventricular area by producing thick fibrous material causing palsies and infarcts.

Hyponatremia:

Syringomyelia due to spinal cord vasculitis.

Potts disease.

Drugs side effects:

- *Isoniazid:*
- Neuropathy, hepatotoxicity
- Rifampicin:
- Hepatotoxicity, orange discoloration of tears, urine, and feaces
- Ethambutol:
- Optic neuritis
- Streptomycin:
- Ototoxicity and vestibular dysfunction

Immune Reconstitution Inflammatory Syndrome:

Paradoxical response to treatment with steroids due to presence of neutrophils in CSF.

Investigations:

Blood tests:

- *CBC:*
- Increase TLC
- Hb (anemia of chronic disease)
- MCV: normal or decrease
- LFTs
- RFTs
- Lactate levels: serum lactate is associated with adverse prognosis.
- HIV serology (sometimes underlying HIV infection causes tuberculous meningitis.)
- ESR
- CRP
- Serum Electrolytes: may show hyponatremia

Urine Lam Test:

Urine based test in which mycobacterial cell wall glycolipid lippoarabinomannan is detected for diagnosis of tubercolosis in HIV patients.

Imaging Studies:

Chest x-ray:

Apical scarring or homogenous opacity as consolidation. Presence of miliary shadows

CT BRAIN /MRI:

Scanned with CamScanner

Patient may develop hydrocephalus in underlying chronic cases

Tuberculoma: shows spread from primary pulmonary TB. Discrete lesion with surrounding edema. Contrast enhancement show ring like lesion and meningeal enhancement can be seen in some cases.

Hypodensities may be noted if stroke is caused by TB in some cases mostly in areas of basal ganglia, midbrain, and brainstem. Half of patients have periventricular infracts.

Optochiasmatic arachnoiditis:

Presence of tuberculous exudates in the areas of suprasellar, perimesencephalic, suprasellar and sylvian fissure with association of vision loss.

CSF Studies:

CSF/RE:

Raised opening pressure

Low glucose usually 1/3rd of serum glucose level.

Protein normal or elevated

Cell count greater than 5 mostly 10-100 micromol/l with predominantly lymphocytes.

Acid fast staining:

Positive in 20 percent of cases.

CSF ADA levels:

Gene Xpert: 30 percent sensitivity in CSF for diagnosis

NGS: Metagenomic next generation sequencing is a new test for diagnosis.

CSF NAAT: use in combination with culture and smear for diagnosis. May use as prognostic tool showing bacterial load.

CSF Culture:

Grown on enriched broth medium for 8 weeks. Considered negative if no growth. Negative in half of the cases.

Needle biopsy of Tuberculoma: but not advisable in most cases

Treatment:

Empirical treatment:

In suspicious cases start ATT with steroids as soon as possible like in TB endemic areas, previous history of extrapulmonary TB, non-compliance to ATT , neck stiffness, radiological evidence supporting diagnosis.

Antituberculous therapy:

Traditional drugs same as used for pulmonary TB. 1st line drugs;

Intensive Phase: 4 Drugs for 2 Months

Isoniazid (5 mg/kg usual max dose 300 mg)

Side effect: neuropathy, liver damage

Rifampin (10 mg/kg usual max dose 600 mg)

Side effect: liver damage

Scanned with CamScanner

Pyrazinamide (18.2 to 25 mg/kg) if weight takes as 50 kg
Side effect: increase uric acid levels
Ethambutol (14.5 to 20 mg/kg) if weight takes as 50 kg
Side effect: optic neuritis
If creatinine clearance is < 30 dose of pyrazinamide and ethambutol is reduced and 3 doses orally per week are given. In case of hemodialysis dose should be given after session.
All are bactericidal with isoniazid with highest CNS penetration while Ethambutol has the lowest

Other first line agents include;

Streptomycin, ethionamide, and levofloxacin

Note:

- Pyridoxine (vitamin B6; 25 to 50 mg/day) is given with isoniazid to avoid neuropathy in
- Pregnant women
- Breastfeeding
- HIV patients
- Alcoholicss
- Malnourished
- CKD
- Advanced age)
- For patients with diagnosed peripheral neuropathy, increasee pyridoxine dose to 100 mg/day.

STEROIDS: used in adjunction with ATT to prevent necrotic cell death of cells infected with mycobacterium tuberculosis. It reduces mortality and reduces recovery time.
Dexamethasone or prednisolone is given for 6-8 weeks.
Dose:
Dexamethasone:
0.3 to 0.4 mg/kg/day (IV) for 2 weeks
Then 0.2 mg/kg/day IV week
Then 0.1 mg/kg/day IV week 4
Then 4 mg per day orally and taper 1 mg off the daily dose each week; total duration approximately eight weeks
Oral prednisolone:
0.5 mg/kg (up to 40 mg/day) may be given for four weeks and then tapered over the following four weeks
Continuous Phase: 2 Drugs for 7-10 Months.
Only isoniazid and rifampicin are continued.

Second Line Drugs:

Used when there is resistance to first-line drugs or in cases of first line drug intolerance or toxicity.

Drugs Safe in Pregnancy:

Scanned with CamScanner

Intensive Phase:

Isoniazid plus vitamin B6, rifampicin, ethambutol for 2 months

Continuation Phase:

Isoniazid and rifampicin for 7-10 months

Note:

All these drugs are safe in lactation too.

Contraindicated drugs:

Streptomycin
Amikacin
Fluoroquinolones
Capreomycin
Kanamycin
Pyrazinamide

Drug Resistant Tuberculosis:

Resistance to one or more first line ATT

Iisoniazid resistant tuberculous meningitis:

Iintensive phase:

Rifampin, ethambutol, pyrazinamide, and a fluoroquinolones for two months

Continuation phase:

Rifampin, pyrazinamide, and a fluoroquinolones for at least 10 months

Poly -drug Resistant TB:

It refers to isoniazid resistance plus resistance to another first-line agent beside rifampicin.

Multidrug Resistant TB:

Resistance to atleast both isoniazid and rifampicin

PRE-XDR:

Rresistance to isoniazid and rifampin as well as a fluoroquinolones (levofloxacin or moxifloxacin

Extensive Drug Resistance (XDR):

Resistance to any fluoroquinolones and atleast one of three second line injectable (kanamycin, capreomycin, and amakacin) in addition to multidrug resistance

Secondary Drug Resistance:

Development of resistance to antituberculous therapy in patients who had previously drug-susceptible TB during or following the treatment

Preventive Therapy In Case Of Tb Contact:

Vaccination of BCG is advisable.

Isoniazid once daily for period of 6-9 months is recommended.

Scanned with CamScanner

Cauda Equina Syndrome and Connus Medullaris Syndrome

Cauda equina syndrome: condition where end fibers of spinal cord are damaged. (Acute lumbosacral radiculopathy).

50 year old man presented with sudden onset of severe back pain radiating to left leg . He was also having sensation of numbness in same leg as well. Along these issues he was having sexual dysfunction , bowel and bladder incontinence and a feeling of reduced sensation along buttocks and genitalia. On examination hypotonia was noted ,reflexes were diminished in lower limbs with power 3/5 noted globally and loss of anal tone was noted with paresthesia in the perianal region.

Investigations:

Mainly the diagnosis is clinical and symptomology depends upon the nerve root that is affected. L5 and S1 radiculopathies are most common.

General examination of the spine important for looking congenital abnormalities E.g nevi, tuft of hairs, vertebral column shape etc.

BEDSIDE MANEUVERS :

Straight Leg Test:

Lasegues sign (worsening of radicular pain on straight leg test) And Browstring sign (relief of radicular pain when knee is flexed during positive straight leg test).

Others ;

Contralateral Straight Leg Test:

Reverse Straight Leg Test:

Patricks test:

Neuroimaging:

MRI lumbosacral spine:

Gold standard that shows compression of cauda equina nerves due to intervertebral disc herniation, degenerative spondolysis, tumor, or non- compressive mechanism like trauma, vascular disease, and inflammation. Ideally MRI with contrast is is best to perform.

CT lumbosacral Spine :

For seeing bone pathology in which MRI could not be done.

CT Myleography

Done where CT is non -conclusive and MRI cannot be done .

Nerve Conduction Studies and Electromyography:

Shows abnormalities in respected muscles that are innervated by the effected nerve root.

Somatosensory Evoked Potentials (SEPs):

Used to localize sensory nerve abnormalities . .

Cerebrospinal Fluid Analysis: Done in cases where radiculopathy is due to neoplastic or infectious etiology. E.g tuberculosis , herpes etc.

NERVE	SYMPTOMS

Scanned with CamScanner

ROOTS	
L1	Numbness and pain in inguinal region
L2-L3-L4	Back pain radiating to anterior of the thigh (sometimes medial lower leg) with sensory loss over the area with weak hip flexion plus adduction and knee extension e.g inability to get up from a chair. Loss of patellar reflex
L5	Backpain radiating to lateral thigh plus buttock,lateral calf and dorsum of foot and great toe . Sensory loss in lateral calf , dorsum of the foot and web space between first and second toe .there is weakness of hip abduction,knee flexion, foot dorsiflexion, toe extension and flexion, foot inversion and eversion. Loss of hamstring reflex. Tibial ridging on examination and dragging of the toes on walking.
S1	Backpain radiating to buttock, lateral thigh ,calf and foot with loss of sensation lateral calf and plantar aspect. Weakness of hip extension, knee and plantar flexion with loss of achilles reflex
S2-S3-S4	Pain in sacral region plus buttock and perineum plus radiating to posterior of the leg with loss of sensation over medial buttock and perianal region along urinary fecal incontinence with sexual dysfunction and loss of anal wink

DIFFERENTIAL DIAGNOSIS :

All pathologies that can cause low back pain ;
Lumbosacral plexopathy , diabetic amyotrophy, and pathologies affecting femoral, tibial, sciatic, and peroneal nerves. Osteprotic compression fracture, osteomylitis , epidural abscess.
Referred pain due to infections , malignancies in abdomen or pelvis can also mimic such pain.

TYPES OF CAUDA EQUINA SYNDROME:

Two types:
CES-R: where there is urinary retention
CES-I: incomplete voiding and poor urinary stream

MANAGEMENT OF CAUDA EQUINA SYNDROME:

Depends upon etiology:
If infection : antibiotics

Pain killers:

Oxycodone after surgery . Other include acetaminophen and ibuprofen

Steroids :

To reduce inflammation and swelling

Acute cases :

Surgery should be done within 48 hours .
Requires surgical decompression by procedure called lumbar laminectomy.
Inoperable cases:
E.g malignant disease radiation and chemotherapy.

Connus Medullaris Syndrome

Connus Medullaris Syndrome: compressive damage to the spinal cord between T12 -L2.

Scanned with CamScanner

55 years old male presented to emergency with sudden onset of excruciating backache with loss of bowel and bladder control and erectile dysfunction. He was having feeling of weakness and numbness in his lower limbs. Upon examination it was noted that he was having saddle anesthesia. Power was symmetrically reduced in lower limbs with increased tone and hyperreflexia. MRI lumbosacral spine was done that revealed a mass lesion at the level of L2 vertebrae. Patient was reffered for neurosurgical intervention to relieve compression.

Difference between Connus Medullaris and Cauda Equina Syndrome:

	Conus medullaris	**Cauda equina**
Bbackache	More severe	less
numbness	Symmetrical	asymmetrical
Reflex	Hyperreflexia	absent
Anal tone	Intact	loss
Sphincter dysfunction	Presents early	Presents late
presentation	Sudden and bilateral	Gradual and unilateral
Muscle wasting	Symmetric with less wasting	More pronounced
Impotence	Frequent	Presents at later stage
radiculopathy	Absent	Asymmetric radiculopathy
Neuron lesion	Both upper and lower	Lower motor neuron lesion

Scanned with CamScanner

MOTOR NEURON DISEASE

Motor Neuron Disease: neurodegenerative disease that affects motor neurons that control voluntary muscles of the body.

44 years old male, teacher by profession presented with complaints of weakness in his legs and twitching of muscles. At first, he thought of it as fatigue, however; weakness in the legs progressed to upper limbs as well and later on he began to struggle with simple tasks like gripping a pen or buttoning his shirt. Following few months his condition deteriorated and eventually became wheelchair bound. Eating and speaking affected as well so NG feed was started. (Onset of bulbar symptoms).

On examination, wasting in upper and lower limbs along fasciculation's in limbs and tongue as well. Tone was increased with diminished reflexes in all limbs. No bowel bladder or vision disturbance was noted. The intellect of the patient stayed unaffected.

Investigations: Basically MND is a Clinical Diagnosis and Diagnosis of Exclusion With Supporting Investigations.

All blood tests including serum electrolytes

- ESR
- CRP
- CALCIUM
- PHOSPHATE
- ANA
- RA Factor
- Vitamin B12
- Anti GM1 Antibody
- Urine Protein Electrophoresis and Immunofixation
- CPK: Elevated upto 1000 units due to denervation.
- CSF R/E. elevated CSF neurofilament

EMG:

Reveals acute and chronic denervation and renervation in multiple muscles.

NCS:

Motor conduction velocities and sensory amplitudes are normal in limbs.

Neuroimaging:

MRI brain, cervical and lumbosacral spine to exclude other diseases.

Differential Diagnosis:

Hereditary spastic paraplegia, post-polio syndrome, hyperthyroidism, myasthenia gravis, multifocal motor neuropathy, cervical radiculomylopathy, benign fasciculation.

TYPES OF MND:

- Progressive bulbar palsy
- Primary lateral sclerosis
- Progressive muscular atrophy

Scanned with CamScanner

- Flail leg syndrome
- ALS plus syndrome (autonomic insufficiency, extrapyramidal, supranuclear gaze paresis, and cerebellar ataxia.)

Management of MND:

Multidisciplinary Approach:

Involves neurologists, physiotherapists. Speech therapists, dietitians, respiratory therapists, nurses and social care workers.

Usually the survival rate is 3-5 years after diagnosis. Palliative care must be provided at all stages of the disease.

Management of respiratory symptoms:

Serial assessments of pulmonary functions to devise a treatment plan .Ventilatory support in case of respiratory failure. Non-invasive positive pressure ventilation is given. Indication for NPPV includes

- Vital capacity less than 50% of predicted value
- Abnormal oxygen saturation at night
- Presence of orthopnea
- Maximal sniff nasal inspiratory force less than 40 cm
- Maximal inspiratory pressure less than minus 60.
- Invasive mechanical ventilation is an option for long duration where needed.

Medication:

Riluzole 50mg is only drug available that decrease progression and increase survival by few months.

Nutrition:

Goal is to increase calories and fluid intakes as insufficiency of nutrients worsen weakness.

Anorexia: (when swallowing is intact)

If primary: appetite stimulants

If due to psychological issue (mood disorder) olanzapine may be given

Dysphagia:

PEG tube placement in case of impaired swallowing. Best before vital capacity falls below 50 percent predicted.

Dysarthria:

Speech therapist and pathologist.

Physiotherapy for Joints and Muscles:

Communication

By writing with pen and paper, electronic communication devices that works with hand and eye control.

Immunizations:

Pneumococcal plus annual seasonal influenza vaccine.

Anxiety:

Psycho-social support, relaxation activities, and reassurance.

Anxiety with Dyspnea:

Scanned with CamScanner

Distressing dyspnea: systemic opioids when symptoms are present despite of NPPV. Benzodiazepine as an adjunct with opioids when there is refractory dyspnea and anxiety is not controlled. No role of oxygen as it worsens hypercapnia.

Fatigue:

Most common symptom. Modafinil is sometimes use.

Associated as a side effect of drug Riluzole. In cases of debilitating fatigue riluzole is withdrawn. Megestrol acetate 499-800mg daily)

Muscle Spasm:

Non- pharmacologic:

Stretching and massage

Pharmacologic:

Mexiletine, levitriacetam, carbamezapine, phenytoin

Spasticity:

Spastic tone is beneficial to continue daily life activities. However excess tone is treated with;

Baclofen: start at 5mg TDS. Max dose 80-120mg per day depending upon tolerance.

Tinzanidine: 2-4mg BD. Max beneficial dose upto 24mg.

Cases resistant to oral drugs;

Botulinum toxin injection with physiotherapy.

Functional Decline and Muscle Weakness:

Use of air mattress to prevent pressure sore.

Specialized eating utensils with holders.

Mobility and assistive devices such as walking frames, canes, crutches, and wheelchairs.

Pseudo bulbar effects: (pathological crying and laughing)

Treatment options: dextromethorphan quinidine (20/10mg).

Tricyclic antidepressant like amitriptyline. Starting dose 10-25mg.

Selective serotinin reuptake inhibitors e.g fluvoxamine 100-200mg daily.

Depression:

Tricyclic antidepressants.

Insomnia:

Nocturnal oximetry to look for oxygen desaturation and need of non- invasive positive pressure ventilation. (NPPV)

Scanned with CamScanner

IMPORTANT SHORT CASES

Cardiology

Follow 6Ps for short cases

- Informed permission
- Explain the procedure to the patient
- Proper position(head end at 45 degree in cardiology short cases) and exposure
- Perform the procedure (examination)
- Place back the patient(to its original position and say thank you)
- And present

Examinations of the precordium consist of the inspection, palpation and auscultation.

Inspection

Look for built, SOB, chest deformity, scar mark, cyanosis, prominent chest veins due to superior vena cava obstruction and pulsation (apex beat, parasternal → RVH , left 2nd intercostal space →due to dilatation pulmonary artery, right 2nd intercostal space→ aneurysm of aorta and epigastrium may be normal in thin lean indiduvals, or RVH and pulsatile liver in Tricuspid regurgitation)

Palpation

Apex beat and its character(normal apex beat is neither heaving nor tapping) , tapping (forceful than normal but palpating fingers are not displaced) and heaving (forceful and palpating finger is lifted ,it is further divided into ill sustaining heave that last for short period and occours in MR and TR and well –sustained heave that last longer and occours in AS and systemic HTN, and thrusting apex beat due to volume overload caused by AR and MR) . Palpable heart sound (S1 in MS ,A2 in systemic HTN and P2 in pulmonary HTN) parasternal heave and thrills (palpable murmur and note its site and timing)

Auscultation

- Heart sounds (1st , 2nd , 3rd and 4th heart sounds and their character(intensity and splitting) and other heart sound (opening snap , ejection click , mid –systolic click , prosthetic valve sounds)
- Murmurs and its characters(Timing , intensity and site of maximum intensity , radiation , character , Pitch (high and or low), effect of respiration and effect of posture)
- Pericardial rub and thrill (is present in grade 4/6) so when you say thrill you should mention grade 4/6

Scanned with CamScanner

Relevant examination

- Pulse (Volume and character)and comparing with other pulses BP ,JVP , bases of the lungs (effusion and fine crakles due to heart failure , sacral and pedal edema , liver (congestive hepatomegaly) and peripheral stigmata of infective endocarditis .

Difference B/W arterial and venous pulsation(JVP) in the neck

Clinical feature	Arterial pulsations	Venous pulsations
Waveform	Single waveform	Double waveform (in sinus rhythm)
Respiratory variation	No effect	Inspiration cause in reduction in the waveform
Patient position	No effect	Lying the patient supine will raise the waveform ,making if more visible
Hepato-jugular reflux	No effect	Will raise the JVP waveform
Palpation	Palpable	Not palpable
Compression	Doesn't abolish arterial pulsation	Usually abolishes JVP waveform

Scanned with CamScanner

MITRAL STENOSIS (MS)

As per command, I have examined this man of average height and built who remained cooperative during examination. On examination of the chest, there is visible pulsation in the precordium; however, there is no gross chest deformity, scar marks and prominent veins. Apex beat is palpable in the left 5th intercostal space in the mid-clavicular line and is tapping in character, but there is no thrill, palpable heart sounds and left parasternal heave. First and 2nd heart heart sounds are audible in their respective area, while first heart sound is loud, the 2nd heart sound is of normal intensity .There is an opening snap audible at the apex followed by mid-diastolic rumbling murmur with pre –systolic accentuation, grade 3/6 at the apex that is best heard in expiration with patient in left lateral position, with the bell of stethoscope. Pulse is 70 beats /minute that is regular ,high volume, normal character and synchronous with other pulses .BP is … JVP is not raised and bases of lungs are clear on auscultation .there is no sacral and pedal edema. There are no peripheral stigmata of infective endocarditis .So based on my examination findings mots probably it is case of mitral stenosis.

MS with atrial fibrillation

As per command, I have examined this man of average height and built who remained cooperative during examination. On examination of the chest, there is visible pulsation in the precordium; however, there is no gross chest deformity, scar marks and prominent veins. Apex beat is palpable in the left 5th intercostal space in the mid-clavicular line and is tapping in character; there is left parasternal heave and thrill. First and 2nd heart heart sounds are audible in their respective area, while first heart sound is of variable intensity, however it is predominantly loud, the pulmonic component of 2nd heart sound is also loud .There is an opening snap audible at the apex followed by mid-diastolic rumbling murmur, grade 3/6 at the apex(it is very difficult to appreciate the diastolic murmur in atrial fibrillation) that is best heard in expiration with patient in left lateral position, with the bell of stethoscope. In addition, there is also Pansystolic murmur at left lower sternal border that is loud during inspiration and early diastolic murmur at the pulmonic area that is also louder in inspiration. Pulse is beats /minute that is irregular, low volume, normal character and synchronous with other pulses .BP is … JVP is raised and there are bibasal crepitation on lung auscultation .there is pedal edema. There are no peripheral stigmata of infective endocarditis and no neurological deficit .So based on my examination findings mots probably it is case of mitral stenosis complicated by pulmonary HTN and atrial fibrillation

Mixed Mitral valve Disease (MS and MR)

You should be able to detect both and determine clinically which one is predominant lesion (like if apex beat is displaced and thrusting and first heart sound is soft, Pansystolic murmur radiate to the axilla and also there is mid-diastolic rumbling murmur at the apex etc then say it is mixed valve lesion (MR and MS) predominantly MR and vice versa and would like to do echo to confirm it)

What are the DDs of mid-diastolic murmur?

- Left atrial mass
- Left atrial thrombus

Scanned with CamScanner

- Severe mitral regurgitation (due to increased forward flow across the mitral valve)

What are the causes of MS?

- Rheumatic heart disease (most common)
- Non –rheumatic causes
  - Congenital
  - Carcinoid
  - Drug induced like Methysergide
  - Mucopolysaccharidose
  - SLE

How will you assess the severity of mitral stenosis clinically?

- Low volume pulse
- Loud S1(sometime S1 may be soft despite severe mitral stenosis)
- Early opening snap
- Increasing length of murmur (not the intensity)
- Signs of pulmonary HTN
- Short interval of A2- opening snap

What is the cause of apex beat tapping?

It is due to loud first heart sound

Why 1st heart sound is loud in MS?

It is caused by partly the speed with which the left ventricular pressure rises at the time of mitral valve closure and partly by the wide closing excursion of the mitral leaflets.

What is the mechanism of loud first heart sound?

It is due to sudden slammed shut of mobile mitral valve during systole

What is the significance of opening snap?

It indicate that valve cusps are pliable and are not rigid and calcified

What is the mechanism of opening snap?

It is produced due to sudden opening of of mitral valve as a result of high-pressure gradient b/w left atrium and ventricle

What is malar flush (mitral facies?)

It is reddish discoloration of malar prominence due to AV anastomoses. Causes are MS, SLE hypothyroidism, MCTD and cold exposure

Patient who has severe MS on echo but asymptomatic how will you proceed?

Stress echocardiography

Patient who is symptomatic but echo shows mild to moderate MS what would be your next step?

Cardiac catheterization

Asymptomatic married woman who has severe MS want to conceive, will you allow her?

According to WHO recommendation it is contraindicated even if she is asymptomatic

What are the complications of mitral stenosis?

- Arrhythmias like A fib

Scanned with CamScanner

- Pulmonary HTN
- Thromboembolism like stroke
- LA thrombus
- Infective endocarditis
- Pulmonary apoplexy
- Right heart failure
- Hoarseness of voice (ortner syndrome)
- Dysphagia due to enlarged left atrium

What are the differentials of early diastolic sounds?

- opening snap
- pericardial knock
- tumor plop
- third heart sound (S3)

What are the other causes of loud first heart sound (S1)?

- WPW syndrome
- Exercise
- High cardiac output states including anemia, pregnancy,
- Left atrial myxoma
- Tachycardia

What are the causes of soft first heart sound (S1) in patients with MS?

- Flail mitral valve
- Calcified mitral valve leaflet
- Concomitant sever aortic regurgitation
- Concomitant mitral regurgitation

What are DDs of low pitch heart sounds?

- Tumor plop
- Mid – diastolic murmur of MS
- Third heart sound
- Fourth heart sound (S4)

What are the DDs of high-pitched heart sounds?

- Opening snap
- Pericardial knock
- Murmurs of MR, AS, AR, HOCM AND MVP
- Second heart sound (S2)
- First heart sound (S1)

What are the clinical features of atrial fibrillation?

Scanned with CamScanner

- pulse deficit of >10 beats / min (less than 10 beats /min suggest PVCs or multifocal atrial tachycardia)
- variable intensity of first heart sound (S1)
- irregularly irregular pulse

What are the DDs of irregularly irregular rhythm?

- Atrial fibrillation
- Ventricular ectopic beats
- Atrial ectopic beats
- Multifocal atrial tachycardia
- Atrial flutter with variable conduction

DDs of variable intensity of first heart sound (S1).

- Atrial fibrillation
- Pulses alternans
- Second-degree (wenckebach) heart block
- Complete AV dissociation
- Flutter with variable conduction

What is presystolic accentuation of murmur? What is the importance?

An increase in the intensity of the murmur in late diastole following atrial contraction due to ↑ flow across the stenosed valve. It indicates that the patient is in sinus rhythm with intact atrial contraction.

What is lutembacher syndrome?

When rheumatic mitral stenosis is associated with secundum atria septal defect it is known as lutembacher syndrome.

What is pulmonary apoplexy?

It is characterized by sudden massive hemorrhage / hemoptysis due to the rupture of thin walled and dilated bronchial veins when there is sudden increase in left atrial pressure.

What is welkin-scoring system? How do you interpret it?

- subvalvular thickening
- leaflets calcification
- leaflets thickening
- leaflets mobility

Each component has grading from 0-4. Total score is 16, score of < 9 favors PTMC, Score > 11 favour surgery while score 9-11 is a gray zone.

How will you classify the severity of MS based on mitral valve area?

Normal cross-sectional area of Mitral valve (MVA) is 4-6 cm^2

Mild > 1.5 cm^2, Moderate 1-1.5 cm^2, severe < 1.0 cm^2 while latest CMDT classification is as below

- **Progressive MS** → (MVA > 1.5 cm^2, mean pressure gradient ≤ 5 mmHg and T ½ < 150 msec)
- **Severe MS** → (MVA ≤ 1.5 cm^2, mean pressure gradient > 5mmHg and T ½ ≥ 150 msec)

Scanned with CamScanner

- **Very Severe MS** → (MVA ≤ 1.0 cm^2, mean pressure gradient > 10 mmHg and $T_{½} \geq 220$ msec)

How will you manage this patient?

After detailed HX and relevant examination, I would like to order some investigation

- **CBC** (anemia → worsen the symptoms and TLC)
- **Coagulation profile**
- **ECG**
  - P –mitrale
  - RVH
  - A-fib
- **Chest X-ray**
  - Double right heart border (left atrial enlargement)
  - Splaying of the carina
  - Pulmonary congestion
  - Prominent pulmonary arteries
  - Kerley B lines
- **ECHO**
  - To confirm the diagnosis
  - To assess the severity
  - To determine etiology
  - To assess and grade pulmonary HTN
  - To look for intracardaic thrombus
  - To determine the suitability for intervention
- **TTE**
  - To exclude LA/LAA thrombus before PTMC/PMBC
- **Coronary angiography**
  - To exclude CAD

How will you treat this patient?

Medical treatment

- BB
- CC
- Digoxin
- Ivabradine (in sinus rhythm)
- Diuretics
- Anticoagulation
- Prophylaxis for rheumatic MS

Surgical treatment

What are the Indication for surgery?

- Symptomatic patient
- Pulmonary congestion

Scanned with CamScanner

- Pulmonary HTN
- Hemoptysis
- Recurrent thromboembolism events despite therapeutic anticoagulation

What are the surgical options?

- PTMC/PMBC
- Surgical repair (preferred over valve replacement)
- Mitral valve replacement)

Surgical repair can be done in two ways

- Closed commissurotomy (lateral thoracotomy approach)
- Open commissurotomy(midline sternotomy approach)

What are the criteria for valvuloplasty (PTMC/PMBC)?

- Mobile valve (opening snap and loud first heart sound)
- No or minimal calcification of the valve and subvalvular apparatus
- Absence of MR and
- Absence of left atrial thrombus (on TTE)

Contraindication of PMBC /PTMC? (Indications for mitral valve replacement)

- MVA> 1.5 cm^2
- More than mild MR
- Presence of left atrial thrombus
- Severe or bi-commissural calcification
- Concomitant CAD requiring CABG
- Absence of commissural fusion
- Severe aortic valve disease or mixed severe tricuspid stenosis and regurgitation

Complications of PMBC/PTMC?

- Acute MR
- Embolization
- Cardiac perforation
- Residual ASD

Recommended INR for mitral valve is 2.5-3.5

DOACs are not recommended for mitral valve

Factors Favors Mechanical Valve	Factors Favors Bio prosthetic Valve
Age <65 years	Age ≥65 years
No contraindication to anticoagulation	Anticoagulation is contraindicated
Any other indication of anticoagulation (A.Fib, Concomitant mechanical valve)	Anticoagulation cannot be managed
	Anticoagulation is not desired by the patient

Scanned with CamScanner

MITRAL REGURGITATION (MR)

(MR without pulmonary HTN)

As per command, I have examined this man of average height and built who remained cooperative during examination. On examination of the chest, there is visible pulsation in the precordium; however, there is no gross chest deformity, scar marks and prominent veins. Apex beat is palpable in the left 6th intercostal space just lateral to the mid-clavicular line and is thrusting in character, but there is no thrill, palpable heart sounds and left parasternal heave. First and 2nd heart heart sounds are audible in their respective area, while first heart sound is soft ,however , 2nd heart sound is of normal intensity .There is high pitch ,soft and blowing Pansystolic murmur of grade 3/6 with maximum intensity at the apex that gets louder during expiration and radiate to axilla . Pulse is 70 beats /minute that is regular ,high volume, normal character and synchronous with other pulses .BP is 140/70 (wide pulse pressure) JVP is not raised and bases of lungs are clear on auscultation .there is no sacral and pedal edema. There are no peripheral stigmata of infective endocarditis .so based on my examination findings mots probably it is case of mitral regurgitation

DDs

- **TR and**
- **VSD** →can be heard throughout the precordium but loudest at the left lower parasternal edge and may cross the mid-line

Differentiating MR and TR clinically

Clinical signs	Mitral regurgitation	Tricuspid regurgitation
Pulse	Normal or jerky(if severe)	Normal
JVP	No specific association	Systolic v waves
Palpation	Apical systolic thrill Thrusting displaced apex	Parasternal systolic thrill Parasternal heave
Auscultation	Pansystolic murmur loudest(in the apex) during expiration ,radiating to axilla	Pansystolic murmur loudest(at tricuspid area) during inspiration, no radiation to axilla
Hepatomegaly	No specific association	Pulsatile hepatomegaly

Radiation of the murmur of MR

Most commonly to axilla, however if

- Rupture of the anterior leaflet of chorda tendineae→ murmur radiate to axilla and back
- Rupture of the posterior leaflet of chorda tendineae→ murmur radiate to cardiac base(parasternal edge) and carotid arteries (Neck)

What are the causes of MR?

Causes may be divided into either primary or secondary or acute and chronic causes

Primary causes (affect valve or subvalvular apparatus)

- Mitral valve prolapse (most common)
- Rupture of chordae tendineae due to IE , trauma and MI

Scanned with CamScanner

- Rheumatic fever
- Marfan syndrome , Ehlers-Danlos Syndrome etc

Secondary causes (functional)

- Left ventricular dilation
- Cardiomyopathies

Chronic MR

- Rheumatic Fever ,MVP , IE , RA , SLE Papillary muscles dysfunction , ankylosing spondylitis , Marfan's syndrome and cardiomyopathies
- Valvotomy or valvuloplasty

Acute MR

- Trauma or surgery
- Infective endocarditis
- Rupture of chordae tendiane(due to IE ,MI and acute rheumatic fever)

What are the Clinical Signs of severity of MR?

- Displaced apex beat
- Precordial thrill
- Soft 1st heart sound
- 3rd and 4th heart sounds
- Widely split second heart sound
- Mid-diastolic flow murmur
- Signs of pulmonary HTN and congestion

Isolated 3rd heart sound, thrusting and length of the murmur is not markers of severity

What are the ECHO signs of severe MR?

- Vena contracta(VC) $\geq$ 0.7 cm
- Regurgitant volume (RVol) $\geq$ 60 mL
- Regurgitant fraction(RF) $\geq$ 50%
- Effective regurgitant orifice (ERO) $\geq$ 0.40cm^2

What is carpentier's classification of MR?

It describe the mechanism of MR

Type 1	Normal leaflet movement	Annular dilatation, Perforation
Type II	Excessive leaflet movement	MVP, Trauma, Rheumatic Heart Diseases (Flail, Prolapse)
Type IIIA	Restricted valve opening	RHD, Carcinoid, SLE
Type IIIB	Restricted valve closure	Dilated Cardiomyopathy, Ischemic cardiomyopathy

How will you investigate this patient?

- **CBC** →HB (anemia worsen pulmonary congestion) TLC (may suggest infective endocarditis)

Scanned with CamScanner

- ECG → may show A-fib , left atrial hypertrophy and left atrial dilatation
- CXR →double heart border, splaying of the carina , cardiomegaly and pulmonary congestion
- ECHO→ to confirm the diagnosis , determine the cause , assess the anatomy of the valve , severity of MR as mentioned above , RT & LT ventricular function and pulmonary HTN
- Coronary angiography to exclude underlying coronary artery disease(if valve replacement is indicated in men aged> 40)

How will you manage this patient?

I will assess the functional status of patient by taking complete HX; will do relevant examination and investigation (as mentioned earlier)

Medical management for symptomatic treatment

- ACEs/ARBs
- Beta-blocker
- Diuretics

Surgical management

(Where we have two-option repair or replace the valve)

Repair of the valve is preferred if possible over replacement because there is no risk of infective endocarditis, Low risk of mortality (1% compare to 5% of MVR) and thromboembolism, long-term anticoagulation is not required and geometry of the LV is preserved

Factors that favours mitral valve repair

- Adult patients having MR secondary to MVP
- Child or adolescent patient
- MR due to chordal rupture, annular dilatation and due to leaflets perforation

Factors that suggest unfavourable outcomes of MV repair

- Old age
- Disturbed anatomy of the valve
- Calcification of the valve
- Sub-valvular apparatus thickening

Indication of surgery

- Symptomatic MR regardless of the EF
- Asymptomatic patient who have EF <60 % or end-systolic dimension of LV is > 4 cm
- Patient with progressive decline in LV EF and or progressive increase in the LV
- Recently trans catheter edge- to- edge repair TEER (Mitral Clip) is indicated in symptomatic patient at higher surgical risk regardless of whether MR is primary or secondary

Indication of secondary prophylaxis of rheumatic fever in case of rheumatic MR

It should be considered for ≥ 10 years or until the age of 40 years (whichever is longer), or lifelong in high-risk patient and continuous prophylaxis is indicated even after valve replacement.

Scanned with CamScanner

Prophylaxis of IE is recommended for procedures that involves manipulation of gingival tissue. perforation of oral mucosa and periapical region of teeth provided there is

- Previous HX of IE
- Prosthetic valve
- Trans catheter implants
- In case of repair than annuloplasty rings , clips and cords

Management of acute MR

Medical l management

- Diuretics and nitrate →↓ filling pressure
- Inotropic agents and IABP→ to treat hypotension and hemodynamic instability
- Sodium nitroprusside → to ↓ afterload and regurgitation fraction

Surgical

- Valve repair(preferred option)
- Valve replacement

How will you manage secondary MR?

- Cardiac resynchronization therapy (biventricular pacing)
- Guideline directed medical management and therapy (GDMT)
    - RAAS (ACEs , ARBS , ARNI)
    - BB
    - SGLT2 inhibitors
    - BI-ventricular pacing
    - Spironolactone

Follow up ech for MR

- Mild MR 3-5 years
- Moderate MR 1-2 years
- Severe MR 6-12 months
- If LV is dilating then assess more frequently

See also CMDT tables for management

Determination of predominant mitral pathology		
	Mitral stenosis	**Mitral regurgitation**
Pulse	Small volume	Normal volume or Hyperdynamic
Blood pressure	Usually unhelpful	Usually unhelpful
Apex	Not displaced Tapping	Displaced Thrusting
Heart sound	Loud S1	Soft or absent S1
Murmur	Rumbling Mid – diastolic	Blowing Pansystolic

Scanned with CamScanner

MITRAL VALVE PROLAPSE (MVP)

There is a mid- systolic click followed by a late systolic crescendo-decrescendo murmur with maximum intensity at the left lower sternal border with diaphragm of stethoscope that is augmented by handgrip .In relevant examination you should look for evidence of associated condition like

- Marfan's syndrome (high-arched palate , arm span > height ,pectus excavatum and scoliosis
- Ehler –Danlos syndrome (hyper extensible skin and joints and blue sclera
- SLE (butterfly rash)
- Osteogenesis imperfect(blue sclera, deafness (hearing aid)
- Polycystic kidney disease (abdominal distension)
- Hyperthyroidism

What is prevalence of MVP ?

5-10% most commonly in female

What are the typical symptoms of MVP?

- Palpitation(most common)
- Anxiety ,SOB and atypical chest pain

What are the DDS of MVP murmurs ?

- Aortic stenosis
- Pulmonic stenosis
- HOCM
- Trivial MR

What are the complications of MVP ?

- Progression to MR
- Heart failure
- Sudden death
- Endocarditis
- Stroke
- Chordal rupture
- Arrhythmias (due to prolong QT interval)

Do these patients need endocarditis prophylaxis ?

Infective endocarditis prophylaxis is no longer recommended in-patient with MVP .

What are the manoeuvres that increase or decrease the duration of murmur ?

Manuvers that increase the duration of murmur and click of the MVP

- Standing
- Dehydration
- Valsalva
- Amyl nitrate

Manuvers that decreases the duration of murmur and click of the MVP

- Squatting

Scanned with CamScanner

- Phenylephrine infusion

Which segment of the mitral valve is commonly affected ?

Posterior middle scallop

How to differentiate B/W MVP and Bicuspid aortic valve ?

Bicuspid aortic valve click coincide with carotid upstroke while MVP click is appreciated after carotid upstroke

How will you investigate this patient ?

- **ECG**
  - Usually normal
  - Non-specific T and ST changes
  - P-mitrale , RVH , LVH and A-Fib and flutter in case of severe MR
- **Chest X-ray**
  - Usually normal
  - Or same findings as discussed in MR
- **ECHO**
  - To confirm the diagnosis
  - To look for etiology
  - To look for other valvular lesion
  - Assess the MR severity
  - Intracardaic thrombus

How will you treat this patient ?

- If asymptomatic → reassurance and follow –up ECHO
  - MVP without MR → every 3-5 years
  - MVP with MR → annually
- If symptomatic , treat conservatively
  - Palpitation→ Beta blocker
  - A-fib → anticoagulation if indicated
  - Arrhythmias → anti-arrhythmic
  - Stroke →aspirin
  - Symptomatic Severe MR → see MR management

Scanned with CamScanner

PROSTHETIC MITRAL VALVE

Look for mid-line sternotomy scar and most patient are left with pulmonary HTN

- On examination of the precordium, there is a mid-line sternotomy scar and on auscultation, there is a prosthetic click at the first heart sound and the 2nd heart sound is normal. No peripheral stigmata of infective endocarditis .pulse is regular or irregular My diagnosis is mitral valve replacement, which seems to be functioning
- Next scenario could be is mitral valve replacement, which seems to be functioning and there is evidence of pulmonary HTN
- Mitral valve replacement and also murmur of MR that suggest it is leaking with signs of pulmonary congestions ± pulmonary HTN

How do you know prosthetic valve is functioning well?

Because there is audible click without added sound

What could be the possible reason for mitral valve replacement?

If apex beat, displaced and tapping then I believe it was MS and if apex beat is displaced and thrusting than possibly it was a regurgitant pathology

What are the types of prosthetic valves?

It is broadly classify into mechanical valve and bio prosthetic valve

Mechanical valve

- Caged Ball (star-Edward) –silicon Ball
- Tilting disc (Bjork and Medtronic Hall)
- Bileaflet (On-x, Medtronic and Carbomedics)

Bioprosthetic Valve

- Autograft (in young patient for replacing infected valves as they are resistant to reinfection)
- Homograft (cadaveric)-stentless
- Heterograft (TAVR , stentless bio prosthesis)

What are the complications of prosthetic valves?

- Infective endocarditis
- Coagulopathy thromboembolism
- Valve dysfunction (thrombosis and dehiscence)
- Hemolysis
- Conduction issues

How will you suspect prosthetic valve obstruction or thrombosis?

This will be suspected if patient is non –compliance to anticoagulation therapy and there is acute onset of symptoms like SOB, chest pain and or an embolic event like stroke

How ll you investigate prosthetic valve obstruction or thrombosis?

- TEE (to see intracardiac mass or immobile valve)
- Cinefluroscopy and 4D CT

How will you treat it?

Scanned with CamScanner

Patient is started on heparin and warfarin is continued unless surgery is warranted

Thrombolytic therapy is treatment of choice for right sided valve thrombosis while surgery for left sided valve thrombosis .However if surgery is not indicated for whatever reason then thrombolytic therapy should be an option for left sided vale thrombosis or when thrombus is small size. This procedure should be carried out in high dependency unit and should be stopped if there is no improvement in hemodynamic after 24-72 hours where surgery may be considered after 24 hours hours' discontinuation of the thrombolytic therapy.

What is the target INR in prosthetic mitral valve?

Mechanical valve → INR 3 .0 and if anitpaletelts is indicated than add aspirin 75-100mg

Bioprosthetic valve → INR 2.5 for 3-6 month warfarin and lifelong aspirin 75-100mg. Only warfarin should be given while NOACs are not indicated. Additionally, if there is a thromboembolic event despite the fact patients have target INR you should increase INR to 4 or add aspirin 75-100mg for mechanical mitral valve and for Bioprosthetic mitral valve who is already on anitpaletelts agent it (antiplatelet) should be switch with warfarin

Scanned with CamScanner

AORTIC STENOSIS

As per command, I have examined this man of average height and built who remained cooperative during examination. On examination of the chest, there is visible pulsation in the precordium; however, there is no gross chest deformity, scar marks and prominent veins. Apex beat is palpable in the left 5th intercostal space in the mid-clavicular line and is heaving in character (there is systolic thrill at the aortic area). First and 2nd heart heart sounds are audible in their respective area, first heart sound is of normal intensity, however, aortic component of the 2nd heart sound is soft .There is high pitch harsh ejection systolic murmur of grade 3/6 heard throughout the precordium with maximum intensity at the A1 area that is augmented by respiratory phase of respiration and radiate to carotid . Pulse is 70 beats /minute that is regular ,low volume, slow rising in character and synchronous with other pulses .BP is ….(narrow pulse pressure), JVP is not raised and bases of lungs are clear on auscultation .there is no sacral and pedal edema. There are no peripheral stigmata of infective endocarditis .Based on my examination findings, mots probably it is case of aortic stenosis

DDs

- **HOCM** →(it is not HOCM because HOCM having maximum intensity at left lower sternal border and augment with certain manuvers)
- **VSD**→(it is not VSD because VSD murmur is Pansystolic and having maximum intensity at left lower sternal border)

What are the causes of aortic stenosis ?

- Bicuspid aortic valve (most common cause in the young)
- Degenerative calcification (….. in the elderly)
- Congenital
- Rheumatic heart disease
- While the rare causes are alkaptonuria, hyperuricemia and as sequelae of infective endocarditis

What are the differentials of murmur that is heard throughout the precordium ?

- AS
- HOCM
- VSD

What are the DDs of ejection systolic murmur that is augmented in expiration ?

- Aortic stenosis
- HOCM
- Supravalvular aortic stenosis also known as William's syndrome)

What is the pulse character in aortic stenosis?

Pulse is slow rising with late peaking and it is also called pulsus Parvus et Tardus

What are the clinical signs of severe aortic stenosis/ what are the signs of severity ?

Peripheral signs

Scanned with CamScanner

- Low volume pulse , Slow-rising pulse and Narrow pulse pressure

Heart sounds

- Soft /absent aortic component of the 2nd heart sound , presence of S4 and reverse splitting of the 2nd heart sound

Murmur

- Late systolic peaking of a long murmur

Hemodynamic consequences

- Displaced apex beat , signs of pulmonary HTN and congestion (heart failure)

Others

- Heaving apex and systolic thrill

What is Gallavardin Phenomenon?

When the murmur of aortic stenosis is heard all over the precordium with highest intensity at the apex, it is called Gallavardin Phenomenon .It is important because this may falsely suggest mitral regurgitation .It is differentiated by quality of murmur (MR →Pansystolic VS. ejection systolic murmur in AS) and hand grip (it make the AS more loudly) .Additionally, soft S1 may point toward MR while soft S2 toward AS.

How will you manage this patient?

After detailed HX and relevant examination, I would like to proceed with

Investigations

- CBC → anemia (Heydes's syndrome)
- ECG
    - LVH with or without strain
    - Rhythm
- CXR
    - May be normal or
    - Cardiomegaly (late feature)
    - Post-stenotic dilatation of proximal ascending aorta
    - Calcification of aortic root
    - Notching of the ribs (in Coaractation of aorta associated with bicuspid valve)
    - Pulmonary congestion (heart failure)
- ECHO for
    - To confirm the diagnosis
    - To assess Severity (see below)
    - Etiology and hemodynamic status
- Coronary angiography (indications)
    - If age > 40
    - Age < 40 but either LV dysfunction or risk factors for IHD
    - Patient undergoing for valve replacement to exclude concomitant coronary artery disease
- Cardiac catheterization

Scanned with CamScanner

- It is carried out when there is discrepancy between symptoms and ECHO information of AR severity

How do you classify the severity of aortic stenosis?

It is based on pressure gradient and aortic valve area

Pressure gradient

Mild → < 20 mmHg (velocity 2.0-2.9m/s), moderate 20-40 mmHg (velocity 3-3.9m/s) and severe > 40 mmHg (velocity ≥ 4 m/s)

Valve surface area (normal is 3-4cm²)

Mild > 1.5 moderate 1.5-1 cm^2 and severe < 1cm^2

What is the AHA classification of AS?

- Stage A

At risk of AS

- Stage B

Progressive AS

Includes mild and moderate AS

- Stage c

Asymptomatic severe AS

C1 → normal EF

C2 →reduced LVEF <50%

- Stage D

Symptomatic severe AS

D1→ Symptomatic severe high gradient AS

D2 →symptomatic severe low gradient AS with reduced LVEF <50%

D3→ symptomatic severe low flow AS with normal LVEF

What are the complications of AS ?

- Sudden death , angina , syncope , arrhythmias , heart block ,LVF ,anemia (Hyde's syndrome) and infective endocarditis

Treatment Aortic valve replacement (AVR) is the only definitive treatment. It can be done via surgical aortic valve replacement (SVAR) which is an invasive procedure or via trans -Cather aortic valve replacement (TAVR)/ Cather aortic valve implantation (TAVI), a minimal invasive procedure which is now first line treatment .

Indications (stage D1-3, C2 and stage C1 with other indication for cardiac surgery)

- If patient is symptomatic
- Asymptomatic patients with severe aortic stenosis (aortic valve area is <1 cm^2) should undergo intervention if they fulfilled any of the following criteria
  - If patient is candidate for another cardiac procedure like CABG
  - When EF is less than 50%
  - Mean pressure gradient is > 55 mmHg
  - Severe valve calcification

Scanned with CamScanner

- Exercise intolerance or when BP fall more than 10 mmHg
- Evidence of rapid increase in aortic gradient (> than 0.3 m/sec /year)
- Evidence of progressive decline in LVEF

- Also read ross , Bentall and Wheat procedures for aortic stenosis
- Medical therapy is ineffective to reduce the progression of the aortic stenosis

What are the types of prosthetic valves?

- Mechanical valve (SVAR)
- Bio prosthetic valve (SVAR and TAVI)

How will you select valve type for a patient?

- Mechanical valve is preferred in-patient who is less than 50 year old and has no contraindication to anticoagulation.
- Bio prosthetic valve is indicated for patients of any age for whom anticoagulation therapy is contraindicated ,not desired or cannot be managed. Additionally, for patients > 65 years of age, bio prosthetic is also indicated.
- For patient 50-65 years of age , choice of valve should be a shared decision

What are the indications of TAVI?

- Patients with symptomatic severe AS who are less than 80 years or younger who have life expectancy < 10 years and no anatomic contraindication to trans femoral TAVI
- Symptomatic patients with severe AS and have high surgical risk at any age and post TAVI survival is > 12 years with adequate quality of life

Anticoagulat

- Bio prosthetic valve → warfarin 3-6 month (INR 2-3) and lifelong aspirin
- Mechanical valve → lifelong warfarin (INR 2-3)

Can we give NOAC to this patient?

NOAC are contraindicated for prosthetic valve

What do you know perform Dobutamine stress echo?

We perform it to

- To assess the severity in low flow low gradient aortic stenosis
- To determine contractile reserve

What is the commonest cause of AS in young patient?

- Bicuspid aortic valve and it is commonly associated with Coaractation of aorta(look for radio-radial delay and radio-femoral delay)and aortic root aneurysm

When aortic root replacement is indicated in bicuspid aortic valve (BAV)?

- Patient with BAV with indication of SVAR having aortic sinuses / ascending aorta diameter is ≥ 4.5 cm is class 2A indication of aortic root repair/ replacement
- Symptomatic or asymptotic patient with BAV having aortic sinuses or ascending aorta diameter >5.5 cm is class 1 indication for aortic root repair/replacement
- Symptomatic patient with bicuspid aortic valve having having of aortic sinuses or ascending aorta diameter > 5.5 cm is class 1 indication of aortic root repair or replacement.

Scanned with CamScanner

How will you differentiate AS from aortic sclerosis?

Features	Aortic Stenosis	Aortic Sclerosis
Pulse volume	Low, slow raising	Normal
Apex beat	Heaving	Normal
Thrill	Systolic	No thrill
A2	Absent or soft	Normal
Ejection systolic murmur	Present, radiates to the neck	Present, usually no Radiation

How will you differentiate AS from HOCM?

Maneuver	Aortic stenosis	HOCM
Valsalva	↓	↑
Squatting	↑	↓
Amyl nitrite inhalation	↓	↑
Standing	↓	↑

In case of mixed valvular disease, you should tell in the description that some of the features are suggestive of AS while some are of AR; however on of the lesion (AR or AS) is predominate (with justification) or say some features are suggestive of AS and some AR as predominant lesion and I would go for echo to confirm the predominant lesion.

Scanned with CamScanner

AORTIC REGURGITATION

As per command, I have examined this man of average height and built who remained cooperative during examination. On examination of the chest, there is visible pulsation in the; however, there is no gross chest deformity, scar marks and prominent veins. Apex beat is palpable in the left 6th intercostal space lateral to the the mid-clavicular line and is thrusting in character .there is no left parasternal heave ,however , there was a diastolic thrill at left upper sternal border. First and 2nd heart heart sounds are audible in their respective area, 1st heart sound is of normal intensity, however, aortic component of the 2nd heart sound is soft .There is high pitch an early diastolic blowing murmur of grade 4/6 best heard at the left sternal edge , that is augmented by patient sitting forward and holding breath after expiration . Pulse is 70 beats /minute that is regular ,high volume, collapsing in character and synchronous with other pulses .BP is ….(wide pulse pressure(systolic –diastolic difference ≥ 60 mmHg), JVP is not raised and bases of lungs are clear on auscultation .there is no sacral and pedal edema. There are no peripheral stigmata of infective endocarditis .Based on my examination findings, mots probably it is case of Aortic regurgitation

What are causes of acute AR ?

- Infective endocarditis
- Acute rheumatic fever (due to valvulitis)
- Trauma
- Dissecting aneurysm affecting ascending aorta
- Prosthetic valve failure

Causes of chronic AR (always exclude DDS in long case and look for relevant features like Argyll Robertson pupil in syphilis and high arched palate in Marfan syndrome)

- **Due to involvement of valve**
  - Rheumatic fever
  - Bicuspid aortic valve
  - Infective endocarditis
  - Trauma
- **Aortic root dilatation**
  - Syphilitic aortitis
  - Marfan's syndrome and Ehler –danlos syndrome
  - Dissecting aneurysm affecting ascending aorta
  - HTN
  - Trauma
  - SLE and RA
  - Seronegative arthritis
  - Pseudoxanthoma
  - Osteogenesis imperfect

What are the clinical signs of severity of AR ?

- Displaced apex beat

Scanned with CamScanner

- Soft/absent S2
- Presence of 3rd heart sound
- Increased duration of murmur
- Signs of heart failure
- Signs of pulmonary congestion
- Wide –pulse pressure (BP) and collapsing pulse
- Peripheral signs (70-75%) sensitive and can be found in other Hyperdynamic circulation

What is the Austin Flint murmur ?

This is a low frequency mid diastolic murmur heard at the apex caused by

- the aortic regurgitant jet impinging on the anterior mitral valve leaflet leading to functional mitral stenosis and
- left ventricular diastolic pressure rising more rapidly than the left atrial pressure

How to differentiate B/W true and functional MS due to AR?

In Austin flint murmur apex beat is displaced ,thrusting soft S1 (may be loud due to Hyperdynamic circulation) and augmented by handgrip while in true MS apex beat is not displaced , tapping ,loud S1 and not affected by handgrip .

What are the causes of wide pulse pressure and collapsing /bounding pulse?

AR, AV fistula, PDA, Hyperdynamic condition like anemia, pregnancy, beriberi and hyperthyroidism

What is the diagnosis if murmur is best heard at 2nd ICS right parasternal border?

- AR due to aortic root dilatation

What is the diagnosis if murmur is best heard at 3rd ICS left parasternal border?

- AR due to primary valve pathology

What is cooing Dove murmur?

It is musical sounds during diastole like coo of dove that occours due to rupture or retroversion of aortic cusp due to trauma, IE, syphilis

Can a Pregnant woman with AR tolerate pregnancy?

Chronic AR is well tolerated as result of the compensatory myocardial and haemodynamic adaptation. Therefore, she can tolerate the pregnancy, as there is ↓ systemic arterial resistance.

How will you manage this patient?

After detailed HX and relevant examination, I would like to proceed with

- **ECG**
  - May be normal
  - LVH ± strain if concomitant AS
- **CXR**
  - Cardiomegaly
  - Valvular calcification
  - Pulmonary congestion
- **CT/MR Aortography**

Scanned with CamScanner

- Assess aortic root and ascending aorta(as bicuspid aortic valve is associated with in 80% cases with Coaractation of aorta)

- **ECHO**
  - To confirm the diagnosis
  - Assess the valve morphology (bicuspid or tricuspid)
  - To determine aetiology of AR
  - To determine the severity of AR (see below)
  - To assess the ventricular size and function
- Cardiac catheterization and coronary angiography

What are the echo findings of Severe AR ?

- EF ≤ 55%
- Vena contracta > 0.6 cm
- LVESD >50 mm
- Regurgitant volume ≥ 60 mL/beat
- Regurgitant fraction ≥ 50%
- Jet width ≥ 65% of LVOT
- ERO ≥ 0.3 cm

When Follow-up echo should be done in-patient with AR?

- 3-5 years for mild AR
- 1-3 years for moderate AR
- 6 monthly for severe AR

Severity of AR based on pressure ½ time

Mild >500 ms , moderate 500-200 ms and severe < 200 ms

Why angina occours in some AR patient ?

- Due to regurgitation , diastolic pressure of aorta is less and as consequence ↓ perfusion pressure of coronary arteries (and ↓)2 supply) of myocardium causing angina .it is an indication for surgery
- During night due to ↑ vagal tone (same MOA as describe above)
- Marked compensatory LVH may also result in angina

Treatment

Medical management

- Treatment of HTN if > 140/90
- If patient cannot undergo surgery than guideline directed medical management for reduced LVEF ,should be treated treated with standard cardiac failure medicine except BB

Why BB should be avoided in patients with AR ?

Because it may precipitate or worsen angina .

BB↓ heart rate that prolong diastolic time that increased the regurgitation time (and volume →↓ aortic diastolic pressure → ↓ coronary perfusion pressure and ultimately reduced 02 to the cardiac muscles that manifest as angina as described previously

Scanned with CamScanner

Surgical management (valve replacement)

- Symptomatic patient (angina and SOB)
- Asymptomatic patient having following
  - EF < 55%
  - LVESD >50 mm
  - LVEDD > 65 mm
  - Progressive ↑ in the size of LV (IIb)
  - Patient undergoing for other invasive cardiac procedure
- Repair of the aortic root(in bicuspid valve) once the root diameter > 5.5 cm regardless of aortic valve disease severity
- **Indication of repair/replacement of aortic root in-patient with a bicuspid aortic valve**
  - Aortic root diameter at sinuses or ascending aorta > 5.5 cm regardless of need for AVR (class 1)
  - Aortic root diameter at sinuses or ascending aorta > 5.0 cm when there are associated risk factors like family HX of dissection , ↑ in the size of 0.5 cm / year , severe HTN and Coaractation of aorta (class IIa)
  - Aortic root diameter > 4.5 cm if patient undergoing AVR (class IIa)

Scanned with CamScanner

What are the peripheral signs of AR?

Quincke's sign	Capillary pulsation in the nail beds-it is of no value, as this sign occurs normally.
Corrigan's sign	Prominent carotid pulsations
De Musset's sign	Head nodding in time with the heartbeat.
Hill.S sign	Increased blood pressure (>20 mmHg) in the legs compared with the arms.
Mueller's sign	Pulsation of the uvula in time with the heartbeat.
Duroziez's sign	Systolic and diastolic murmurs over the femoral artery on gradual compression of the vessel.
Traube's sign	A double sound heard over the femoral artery on compressing the vessel distally.
Mayne's sign	A decrease in diastolic pressure of 15 mmHg when the patient's arm is held above the head compared with that when the arm is at the level of the heart.
Rosenbach's liver pulsation sign	Pulsation of the liver in time with the heartbeat (in the absence of tricuspid regurgitation).
Austin Flint murmur	Short rumbling diastolic murmur, due to functional mitral stenosis caused by impinging of the aortic regurgitant jet on the anterior mitral valve leaflet.
Becker's sign	Accentuated retinal artery pulsations.
Gerhard's sign	Pulsatile spleen.
Landolfi's sign	Prominent alternating constriction and dilation of the pupils,
Lincoln's sign	Exaggerated movement of the ankle when one leg is crossed over the other
Sherman's sign	An easily palpable dorsalis pedis pulse in a patient over the age of 75 years
water hammer pulse	When radial pulse become more prominent on rising the patient arm
Ashrafian's sign	Pulsatile pseudoproptosis

MIXED AORTIC VALVE DISEASE

As per command, I have examined this man of average height and built who remained cooperative during examination. On examination of the chest, there is visible pulsation in the; however, there is no gross chest deformity, scar marks and prominent veins. Apex beat is palpable in the left 6th intercostal space lateral to the the mid-clavicular line and is thrusting in character. First and 2nd heart heart sounds are audible in their respective area, 1st heart sound is of normal intensity, however, aortic component of the 2nd heart sound is soft .There is high pitch an early diastolic blowing murmur of grade 4/6 best heard at the left sternal edge , that is augmented by patient sitting forward and holding breath after expiration .there is also an ejection systolic , heard throughout the precordium but loudest at the A1 area which is augmented by expiration and radiate to carotid . Pulse is in the range of 70 beats /minute that is regular, high volume, collapsing in character and synchronous with other pulses .BP is .... JVP is not raised and bases of lungs are

Scanned with CamScanner

clear on auscultation .there is no sacral and pedal edema. There are no peripheral stigmata of infective endocarditis .Based on my examination findings, mots probably it is case of Mixed Aortic Valve Disease predominantly Aortic regurgitation (and vice versa).

- If you are not sure ask some features are suggestive of AS and some AR as predominant lesion therefore I would like to do echo to ascertain predominant pathology

Clinical sign	Predominant aortic stenosis	Predominant aortic regurgitation
Apex beat	Normal or minimal displaced and heaving	Displaced and thrusting
Pulse character	Slow-rising	Collapsing
Pulse volume	low	Large
Systolic thrill	present	Not present
Systolic murmur	Harsh/loud long murmur ,with late systolic peaking	May be harsh/loud but is usually short , speaking early in systolic
Systolic blood pressure	Low	High
Pulse pressure	Narrow	Wide

Prosthetic aortic valve

- On examination of the precordium, there is a mid-line sternotomy scar and on auscultation, first heart sound is normal while there is prosthetic click with 2nd heart sound at aortic area. No peripheral stigmata of infective endocarditis .pulse is regular or irregular My diagnosis is aortic valve replacement, which seems to be functioning as there is audible click

Primary pathology of replacement

- If apex beat is not displaced →indication of replacement was probably stenosis
- If apex beat is displaced → indication of replacement was aortic regurgitation

Target INR in AVR

- Mechanical AVR with no other risk factors →INR goal 2.5 and if any antiplatelet is indicated than low dose - ASA (75-100mg)
- Mechanical AVR with other risk factors →INR goal 3.0 and if any antiplatelet is indicated than low dose - ASA (75-100mg)
- Surgical bioprosthetic AVR → 2.5 INR with warfarin for 3-6 months and lifelong anti-platelets
- TAVI →2.5 INR with warfarin /dual antiplatelet for 3-6 months and lifelong anti-platelet (ASA 75-100mg daily)

Thromboembolic event in prosthetic AVR despite having target INR

- Mechanical AVR with INR in range →↑ the INR to 3.0 or add ASA 75-100mg (2a)
- bioprosthetic AVR on antiplatelet → add warfarin (VKA anticoagulation) instead of antiplatelet (2B)

Scanned with CamScanner

What is the anticoagulant of choice in pregnancy?

- If the lady is using warfarin < 5mg /24 hour , continue until one week before delivery
- If she uses warfarin >5 mg/day , patient should be switched to LMWH(with monitoring of anti Xa level, target valve is 0.8-1.2U/mL 4-6 hrs after dose) in the first trimester and warfarin in 2nd and 3rd trimsters until before one week of delivery and resume anticoagulation once homeostasis is maintained

IE in valve surgery

- Early IE (< 2 months) is caused by staph epidermis
- Late IE has similar microbiology spectrum to native valve

Indication of surgery in IE

- Fungal infection
- Prosthesis dehiscence or obstruction
- New onset / worsening heart block and heart failure
- Recurrent embolization
- Tissue invasion or fistula formation
- Persistent bacteremia that is resistant to IV antibiotics

Post-Op (valve surgery) atrial fibrillation

- Upto 50% of patient may experience it
- In most cases it is self-limiting and if persist beyond 24 hours than DC cardioversion , short course of anit-arrythmic therapy and anticoagulation may be considered

Scanned with CamScanner

VENTRICULAR SEPTAL DEFECT (VSD)

As per command. I have examined this man of average height and built who remained cooperative during examination. On examination of the chest, there is no visible pulsation in the precordium, gross chest deformity, scar marks, and prominent veins. Apex beat is palpable in the left 5th intercostal space in the mid-clavicular line and is normal in character .there is no, palpable heart sounds and left parasternal heave, however, there is systolic thrill in left lower sternum. First and 2nd heart heart sounds are audible in their respective area .There is high pitch Pansystolic murmur of grade 4/6 audible throughout the precordium that is best heard at left lower sternal border and radiate to right parasternal border . Pulse is 70 beats /minute that is regular ,high volume, normal character and synchronous with other pulses .BP is … JVP is not raised and bases of lungs are clear on auscultation .there is no sacral and pedal edema. There are no peripheral stigmata of infective endocarditis .so based on my examination findings mots probably it is ventricular septal defect with a left to right shunt. Moreover, it is hemodynamically insignificant (as there are no signs of pulmonary HTN and heart failure)

Differential Diagnoses for Holosystolic Murmur:

- **Mitral Regurgitation:**
  - Murmur may also be holosystolic but typically radiates to the left axilla and may be associated with a displaced apex beat.
- **Tricuspid Regurgitation:**
  - Holosystolic murmur heard at the left lower sternal border but usually accompanied by right-sided heart signs.
- **Ventricular Septal Defect:**
  - Characterized by the specific location of the murmur and presence of a thrill.

How will you assess whether the VSD is hemodynamically significant or not?

The presence of pulmonary HTN (loud P2, parasternal heave), LV enlargement (displaced apex beat) / dysfunction (signs of LVF) or ↑ flow across the mitral valve (MDM at apex) suggest that VSD is hemodynamically significant

	Insignificant	**Significant**	**Significant**
Apex	Normal	Displaced and thrusting	Displaced and thrusting
Cyanosis	No	No	Yes
Defect	Small (L→R)	Large (L→R)	Large (R→L)
S_2	A_2_p_2	A_2-p_2 (loud p_2)	Single loud S_2
Clubbing	No	No	Yes
VSD murmur	loud	Less loud	No
Pulmonary hyper tension	No	Yes	Yes

Scanned with CamScanner

How will you know about the direction of shunt clinically?

- If the patient is not cyanosed then the direction is from left to right while in the presence of cyanosis suggest a right to left shunt

What is the relation of size of VSD murmur?

- Very small (pinhole) Size VSD produce soft murmur
- Moderate size VSD produces very loud murmur
- Very large size VSD produces very soft murmur (due to equal pressure in both LV and RV and so no turbulence to produce a murmur)

What is maladie de roger?

A small VSD with a loud murmur at left lower sternal border is called maladie de roger

Classification of VSD by Location:

- **Membranous VSD:**
  - Located in the membranous portion of the interventricular septum.
  - Most common type often associated with a more pronounced murmur and thrill.
- **Muscular VSD:**
  - Located in the muscular portion of the septum.
  - May be single or multiple, and can be more difficult to detect on examination due to variability in murmur location.
- **Outlet VSD:**
  - Located below the pulmonary valve (infundibular VSD)(located where the blood leaves the ventricles .
  - May be associated with outflow tract obstruction, influencing the murmur characteristics. It include membranous , subaortic VSD
- **Inlet VSD:**
  - Located below the tricuspid valve (located where the blood enters the ventricles).
  - Can be associated with other anomalies and may affect the presentation and management approach. It includes AV canal type VSD

Classification of VSD severity based on size

- Small VSD < 3mm
- Moderate VSD 3-5 mm
- Large VSD > 5 mm

What are the causes of VSD?

Acquired

- Ischemia as post MI complication
- Iatrogenic (RV pacing with septal puncture during alcohol septal ablation)

Congenital

Scanned with CamScanner

- Maternal DM, alcohol consumption and phenylketonuria
- Down , Edward and patau,s syndrome

What are the complications of VSD?

- IE
- Ventricular arrhythmias
- Pulmonary HTN and LVF
- Aortic regurgitation
- Eisenmenger syndrome

Investigations:

- **Echocardiography:**
  - Essential for confirming the diagnosis, assessing the size, and location of the defect.
  - Evaluates the left-to-right shunt volume and potential impact on the cardiac chambers.
  - Assesses for any associated lesions or complications.
- **Electrocardiogram (ECG):**
  - May reveal signs of left or right ventricular hypertrophy depending on the size of the shunt and chronicity.
  - May be normal
- **Chest X-ray:**
  - To detect cardiomegaly, increased pulmonary vascular markings, and any signs of heart failure.
- **Complete Blood Count (CBC):**
  - To check for anemia or signs of infection.

Management:

Spontaneous closure of small VSD may occours in 50% of cases by age of 2 years and is uncommon after 4 years. This is frequently seen in muscular and perimembranous VSD types

Medical Management:

- **Diuretics:**
  - Used to manage symptoms of heart failure and reduce fluid overload.
- **ACE Inhibitors:**
  - To reduce afterload and manage heart failure symptoms.
- **Beta-blockers:**
  - For rate control if arrhythmias are present.
- **Endocarditis prophylaxis**
  - Prophylaxis for infective endocarditis is indicated for unrepaired VSD , repaired VSD with residual shunt and 6 months after device closure

Surgical Management

Scanned with CamScanner

We have two surgical options

- Trans catheter device closure
- Hybrid approach

Indications for Surgery:

- LV volume overload
- Large VSD with significant left-to-right shunt causing heart failure
- Progressive pulmonary hypertension(PA systolic pressure is less than 50% systemic pressure and pulmonary vascular resistance is less than 1/3rd of systemic resistance)
- Left ventricular dilation
- Development of aortic regurgitation

Absolute Contraindications for Surgery:

- **Severe Irreversible Pulmonary Hypertension (Eisenmenger Syndrome):**
  - Pulmonary vascular resistance (PVR) > 8 Wood units (or pulmonary arterial pressure > 2/3rd of systemic systolic pressure/ pulmonary vascular resistance > 2/3rd of systemic vascular resistance).
  - Right-to-left shunt with significant cyanosis.
- **Significant Left Ventricular Dysfunction:**
  - Ejection fraction (EF) < 30%.
- **Active Myocardial Ischemia or Infarction:**
  - Recent myocardial infarction (MI) within the last 3 months without stabilization.

Relative Contraindications for Surgery:

- **Severe Right Ventricular Dysfunction:**
  - Right ventricular ejection fraction (RVEF) < 35%.
- **Severe Aortic Valve Disease:**
  - Severe aortic regurgitation or stenosis requiring additional complex procedures.
- **Severe Tricuspid Valve Disease:**
  - Severe tricuspid regurgitation or stenosis impacting surgical outcomes.
- **Severe Systemic Conditions:**
  - **Advanced Chronic Obstructive Pulmonary Disease (COPD):**
    - Forced expiratory volume in 1 second (FEV1) < 50% predicted.
  - **Advanced Renal Failure:**
    - Glomerular filtration rate (GFR) < 30 mL/min.
  - **Severe Uncontrolled Diabetes:**
    - HbA1c > 8%.
  - **Recent Stroke:**
    - Within the last 6 months without recovery.

Potential Complications of VSD Repair:

Scanned with CamScanner

- Residual shunt
- Conduction disturbances (e.g., complete heart block)
- Ventricular dysfunction
- Arrhythmias
- Infection

Eisenmenger Syndrome:

Definition: A condition resulting from a long-standing left-to-right shunt (e.g., VSD, ASD, PDA) causing pulmonary hypertension, leading to reversal of the shunt and cyanosis.

Clinical Features of Eisenmenger Syndrome:

- Cyanosis
- Clubbing
- Murmur of the primary pathology (VSD here) diminish or disappear and new murmur of TR and PR are audible
- Polycythaemia
- Dyspnea on exertion
- Syncope

Management of Eisenmenger Syndrome:

- Avoidance of high altitudes
- Supplemental oxygen
- Anticoagulation (if no contraindications)
- Iron supplementation (if iron deficiency)
- Pulmonary vasodilators (e.g., bosentan, sildenafil)
- Heart-lung transplantation in severe cases

Differential Diagnoses for a Diastolic Rumble at the Apex:

- Increased flow across the mitral valve due to VSD
- Mitral stenosis
- Atrial myxoma

DDs of murmur heard throughout precordium

- Aortic stenosis
- HOCM
    - Ejection systolic murmur at left lower sternum but sometime confused with Pansystolic(sometime there is MR murmur as well) that does not radiate to carotid but upto the sternal edge
    - Heaving apex beat
    - Low volume pulse
- VSD

Approach for Long Case

Scanned with CamScanner

Objective: In a long case, provide a thorough and detailed presentation, including in-depth history, comprehensive physical examination, and a detailed plan for investigation and management.

Introduction:

- **Patient Introduction:** Full introduction including age, presenting complaints, and relevant background.
    - Example: "This is a 7-year-old child who has been referred for evaluation of suspected congenital heart disease. The primary complaints include easy fatigability, recurrent respiratory infections, and growth retardation."

2. History Taking:

- **Presenting Complaints:** Detailed description of symptoms and their progression.
    - Example: "The child has had frequent respiratory infections over the past year and has become increasingly tired, with a noticeable decrease in physical activity and poor weight gain."
- Past Medical History:
    - **Congenital or Cardiac Issues:** Any relevant history or previous evaluations.
        - Example: "No known congenital heart disease. The child has had multiple episodes of upper respiratory tract infections."
- Family History:
    - **Congenital Heart Disease:** Any family history that might be relevant.
        - Example: "No significant family history of congenital heart defects or other genetic conditions."
- Social History:
    - **Living Conditions:** School attendance, exposure to environmental factors, and lifestyle.
        - **Example:** "The child lives with parents in a non-smoking household and attends school regularly."
- Review of Systems:
    - **Comprehensive Review:** Any additional symptoms or relevant findings.
        - Example: "No history of cyanosis, syncope, or chest pain."

Physical Examination:

- **General Inspection:**
    - **General Appearance:** Detailed observation.
        - Example: "The child appears well-nourished but slightly pale. No signs of distress or cyanosis."
- Vital Signs:
    - **Pulse:** Rate, rhythm, and character.
        - Example: "Pulse rate is 100 beats per minute, regular, and of normal volume."
    - **Blood Pressure:** Measure and interpret.
        - Example: "Blood pressure is 100/60 mmHg, appropriate for age."

Scanned with CamScanner

- **Respiratory Rate:** Assessment of breathing pattern.
  - Example: "Respiratory rate is normal, and lung fields are clear."

- **Cardiac Examination:**
  - **Inspection:** Observation of precordium.
    - Example: "No visible chest deformities or abnormal pulsations."
  - **Palpation:**
    - **Apex Beat:** Location and characteristics.
      - Example: "The apex beat is palpable in the left 5th intercostal space at the mid-clavicular line."
    - **Thrill:** Presence and location.
      - Example: "A palpable thrill is noted at the left lower sternal border."
  - **Auscultation:**
    - **Heart Sounds:** Detailed description.
      - Example: "First and second heart sounds are normal, with no abnormal splitting."
    - **Murmur:** Detailed characteristics, including timing and radiation.
      - Example: "A harsh, holosystolic murmur, grade 4/6, is best heard at the left lower sternal border and radiates to the right lower sternal border."

- **Peripheral Examination:**
  - **Edema:** Check for any swelling.
    - Example: "No pedal or sacral edema."
  - **Hepatomegaly/Splenomegaly:** Palpation for organ enlargement.
    - Example: "No hepatomegaly or splenomegaly detected."

Scanned with CamScanner

ATRIAL SEPTAL DEFECT (ASD)

As per command, I have examined this man of average height and built who remained cooperative during examination. On examination of the chest, there is no visible pulsation in the precordium, gross chest deformity, scar marks, and prominent veins. Apex beat is palpable in the left 5th intercostal space in the mid-clavicular line and is normal in character .there is no, palpable heart sounds and left parasternal heave and thrill. First and 2nd heart heart sounds are audible in their respective area .first heart sound is normal while there is fixed wide splitting of the 2nd heart sound. There is an ejection systolic murmur at the left upper sternal edge (pulmonic area) murmur of grade 3/6 and does not radiate. Pulse is 70 beats /minute that is regular, normal volume, normal character and synchronous with other pulses .BP is … JVP is not raised and bases of lungs are clear on auscultation .there is no sacral and pedal edema. There are no peripheral stigmata of infective endocarditis .so based on my examination findings mots probably it is atrial septal defect with a left to right shunt. Moreover, it is hemodynamically insignificant (as there are no signs of pulmonary HTN and heart failure)

DDs (based on murmur)

- **PS and**
- **TOF**

What are other murmurs may be heard in ASP patient ?

- Mid-diastolic murmur at tricuspid area due to left to right shunting of blood resulting in functional stenosis of tricuspid valve
- Murmur of MR (ostium premium associated cleft anterior mitral leaflet)

What are the other causes of widely split 2nd heart sound ?

- Due to early closure of the aortic valve
  - Severe MR
  - VSD
- Due to delayed closure of pulmonic valve
  - RBBB
  - Pulmonic stenosis and regurgitation
  - Hemodynamically significant VSD (pulmonary HTN)

What are the types of ASD ?

- Ostium secundam →70%
- Ostium primum→15%
- Sinus venosus →15%
- Coronary sinus →1%

What are the clinical features of hemodynamically significant ASD?

- Signs of pulmonary HTN
- Mid diastolic flow murmur at left lower sternal border
- Ejection systolic murmur of ≥4/6 grade

Scanned with CamScanner

How will you investigate this patient?

- **CXR**
  - May be normal
  - Oligaemic outer third lung filed
  - Enlarged left atrium
- **ECG**
  - Incomplete RBBB
  - LAD(ostium primum) and RAD (ostium secundam ASD)
  - Inverted P waves in inferior leads (sinus venosus)
  - RVH ,P pulmonale (right atrial hypertrophy) and biphasic P waves in V1-V2 (left atrial enlargement)
- **ECHO**
  - Confirm the diagnosis
  - To determine types of ASD ,direction of flow and Pulmonary HTN
  - To look for other cardiac anomaly
  - RV and LV size and dysfunction
- **TEE**
  - Help diagnose rare type of ASD like sinus venosus
  - Anomalous pulmonary venous return
  - Before percutaneous closure to assess the margin anatomy , device size etc

How will you treat this patient ?

If ASD is small and asymptomatic(hemodynamically insignificant)

- Reassurance

Symptomatic ASD

- **Medical treatment of LVF , pulmonary HTN**

Surgical treatment

- Surgical closure
- Percutaneous device closure

Which option will you select for your patient ?

ASD secundum if the margin is good than device closure is preferable and if margin anatomy is disturbed than surgical repair is indicated .While for all other ASD surgical repair is preferred option

What is the adequate size for device closure ?

- Rest diameter < 35 mm
- Stretched diameter < 41 mm

Name of devices for percutaneous device closure

- The Helex
- The amplatzer septal occlude (ASO)
- The cardioSEAL septal occlude system

Scanned with CamScanner

What are the indications of ASD closure ?

In simple words if patient is symptomatic , having enlarged right heart and mild pulmonary HTN are indication of ASD closure

- Shunt fraction (Qp:Qs) > 1.5
- Shunt fraction(Qp:Qs) < 1.5 with paradoxical embolism
- ASD with right sided overload (RA and RV enlargement)

May be consider in

- Pulmonary vascular resistance (PVR) < 1/3rd of systemic vascular resistance (SVR) and PASP < 50% systolic systemic pressure
- PVR > 1/3rd of SVR and PASP > 50% systolic systemic pressure(IIb)
- PVR > 2/3rd of SVR and PASP > 2/3rd of systolic systemic pressure but Net Left to right shunt or there is evidence of pulmonary resistance reversibility with vasodilator challenge

Treatment after device closure

- No anticoagulation is needed after device closure , however , dual antiplatelet is indicated for 6 months (endothelialisation completed)
- IE prophylaxis is not indicated before surgery , however it is indicated in the following situation
  - Prior HX of IE
  - 6 months after ASD closure with device or prosthetic material
  - In case of residual shunt
  - Patient who have developed Eisenmenger

What are the contraindications for percutaneous ASD closure ?

- Active infective endocarditis
- Inadequate rim < 5mm
- Severe pulmonary HTN
- Any Contraindication for ASD closure
- ASD ostium primum , sinus venosus and coronary ASD

What are the complications of percutaneous device closure ?

Device related complications

IE ,thrombus formation , Device dislodgment and thromboembolism

Procedure related complications

Haematoma formation , atrial perforation and AV fistula at the site

How ASD is different from patent foramen ovale?

In patent foramen ovale, there is no equalization of atrial pressure unlike ASD .

What are the clinical conditions associated with PFO?

- Embolic strokes (especially in young individuals)
- Headaches /migraine
- Platypnea – orthodeoxia syndrome
- Decompression illness in divers and those working at high altitude

Scanned with CamScanner

What are the indications of PFO closure?

- Recurrent cryptogenic stroke despite medical therapy
- Frequent episodes of migraine
- Platypnea-orthodeoxia syndrome

What are the contraindications of PFO closure?

- Severe pulmonary hypertension
- Presence of other congenital heart defect that need correction
- Documented hypercoagulable state
- Hypersensitivity / contraindication to antiplatelet and anticoagulant

Scanned with CamScanner

HYPERTROPHIC OBSTRUCTIVE CARDIOMYOPATHY (HOCM)

As per command, I have examined this man of average height and built who remained cooperative during examination. On examination of the chest, there (no) visible pulsation in the precordium, no gross chest deformity, scar marks, and prominent veins. Apex beat is palpable in the left 5th intercostal space in the mid-clavicular line and having in character .there is systolic thrill at left lower sternum. First and 2nd heart heart sounds are audible in their respective areas (while the 2nd heart sound has reversed splitting but in exam never mention it until you are sure to defend it) .There is an ejection systolic murmur of grade 4/6 audible throughout the precordium that is best heard at left lower sternal border and radiate to radiate to the sternal edge but not to the carotid and augmented by expiration ,valsalva Maneuver and standing from the sitting position while the intensity is reduced by squatting position . There is also a Pansystolic murmur at the apex that radiate to the axilla(due to systolic anterior motion of the mitral valve). Pulse is in the range of 65-70 beats /minute that is regular ,low volume, normal (jerky) character and synchronous with other pulses .BP is … JVP is not raised and bases of lungs are clear on auscultation .there is no sacral and pedal edema. There are no peripheral stigmata of infective endocarditis .so based on my examination findings mots probably it is a case of HOCM

DDs of murmur heard throughout the precordium

- AS ,VSD and HOCM (already discussed in VSD)

Difference B/w hypertrophic obstructive cardiomyopathy (HOCM) and hypertrophic cardiomyopathy

The latter is non –obstructive and majority of them do not have significant resting outflow tract gradient while in former there is significant outflow obstruction due to marked asymmetrical septal hypertrophy and systolic anterior motion of the mitral valve that opposes the interventricular septum during systole

How will you differentiate AS from HOCM?

Maneuver	Aortic stenosis	HOCM
Valsalva	↓	↑
Squatting	↑	↓
Amyl nitrite inhalation	↓	↑
Standing	↓	↑

Additionally , handgrip ,intensity of the murmur of AS is increased while HOCM is decreased due to increased cardiac output

What are the drugs that should be avoided in HOCM ?

- Nitrates
- Digoxin
- ACEs & ARBs
- Inotropes and

Scanned with CamScanner

- CCB (didyropyridine)

What are the risk factors for sudden cardiac death in HOCM ?

- Syncopal attack in the last 6 months
- Family HX of sudden death
- Marked LVH (septal thickness in any segment > 3cm
- Non sustained VT
- LV apical aneurysm
- Drop in the BP during exercise
- LV systolic dysfunction eg EF < 50%

What drug will you prescribed in HOCM patient for A- fib?

Amiodarone and disopyramide (having no concomitant long QT syndromes) .additionally, DOAC (anticoagulation) should be started regardless of CHADSVASc score

What are the complications of HOCM ?

- Sudden death
- Angina
- Heart failure (systolic and diastolic)
- Endocarditis
- Arrhythmias esp ventricular

What are the conditions associated with HOCM ?

- Fabrys,s disease
- WPW syndrome
- Fredric ataxia
- Hereditary lentiginosis

What are the indications of ICD in this patient ?

- Survival of cardiac arrest
- Strong family HX of sudden cardiac death
- Sustained VT
- Ventricular fibrillation

What is Brockenbrough-Braunwald- morrow sign ?

Diminished pulse pressure in post-extrasystolic beat or in other words the LVOT gradient increases in the beat pot premature ventricular beat due to paradoxical ↓ in arterial pressure and ↑ LV contractility post premature ventricular contraction (see 250 cases)

Why there is double apical impulse in HOCM

It is due to presystolic impulse transmission of forceful atrial contraction just before the closure of mitral valve against a highly non-complaint LV and 2nd impulse is due to LV contraction

What is triple ripple cardiac impulse ?

As we discussed in double apical impulse ,along with pres- systolic apical impulse due to atrial contraction and LV apical impulse due to LV contraction , there is a late systolic bulging of apex that occur when heart is almost empty and performing near isometric contraction , there is triple apical impulse called as triple apical impulse

Scanned with CamScanner

How will you manage this patient ?

After detailed HX and relevant examination, I would like to order some investigation

- ECG
  - LVH ± strain and non-specific ST and T wave changes
  - Left atrial enlargement
  - Q waves in inferior leads and I , avL . V2-V6 and atrial fibrillation
- CXR
  - May be normal
  - Cardiomegaly , left atrial enlargement and pulmonary congestion
- ECHO(MR ,SAM , ASH)
  - Confirm the diagnosis
  - Systolic anterior motion of mitral valve
  - Asymmetrical septal hypertrophy(> 15 mm) and MR
  - Dynamic left ventricular outflow obstruction
  - Small LV cavity due to LVH
  - Diastolic(characteristic abnormality) and systolic dysfunction(late)
- Holter monitoring
  - Non-sustained VT and other arrhythmias
- Cardiac MRI
  - Myocardial scar (late gadolinium enhancement) and other finding as discussed above
- ETT
  - Evidence of inducible ischemia and arrhythmias , determine presence of detectable LVOT gradient and BP , HR and rhythm response during exercise
- Right and left heart catheterization

Treatment

Medical treatment

Asymptomatic→ BB

Symptomatic

- BB if not effective than CCB and followed by disopyramide
- Amiodarone for ventricular arrhythmias
- Treat AF
- Diuretics for heart failure

Surgical

- Surgical myomectomy
- Alcohol septal reduction and
- Dual chamber pacemaker(DDD)

Scanned with CamScanner

PULMONARY STENOSIS

As per command. I have examined this man of average height and built who remained cooperative during examination. On examination of the chest, there is visible pulsation in the precordium; however, there is no gross chest deformity, scar marks and prominent veins. Apex beat is palpable in the left 5th intercostal space in the mid-clavicular line and is normal in character . There is left parasternal heave(reflect RV volume overload) and palpable systolic thrill at the pulmonic area . First and 2nd heart heart sounds are audible in their respective area, first heart sound is of normal intensity, however, the 2nd heart sound is widely split with soft pulmonic component of the 2nd heart sound (there may be S4 audible which is due to forceful atrial contraction) .there is systolic click and a high pitch ejection systolic murmur of grade 4/6 heard best heard at the upper left sternal border (pulmonic area) that radiate to the suprasternal notch and augmented by inspiration . Pulse is 70 beats /minute that is regular ,normal volume and character and synchronous with other pulses .BP is .... JVP is not raised and bases of lungs are clear on auscultation .there is no sacral and pedal edema. There are no peripheral stigmata of infective endocarditis .Based on my examination findings, mots probably it is case of pulmonic stenosis

DDS

- AS
- ASD
- HOCM
- TOF

How will you differentiate b/w murmur of pulmonary stenosis and aortic stenosis ?

Clinical features	Aortic stenosis	Pulmonary stenosis
Respiratory variation	Louder in expiration	Louder in inspiration
JVP	Normal unless pulmonary HTN	Prominent tall a wave
Palpation	Left ventricular heave	Left parasternal heave
S2 characteristics	Mild →Normal split Severe →reversed split and soft or absent A2	Widely split S2 with diminished P2 in severe cases
Murmur characteristics	Murmur ends before A2	Murmur can extend beyond A2
Pulse	Low volume and slow rising	Normal volume and character

Scanned with CamScanner

Causes of PS

- **Causes of Valvular stenosis**
  - Congenital
  - Rheumatic heart disease
  - Carcinoid syndrome
  - Noonan' s syndrome
- **Causes of Supravalvular stenosis**
  - Williams syndrome
  - Congenital rubella
- **Causes of subvalvular stenosis**
  - Fallot's tetralogy

What are the clinical signs of severe PS ?(only mentioned the signs that are present in your case)

- Large a wave (JVP) if in sinus rhythm
- Left parasternal heave
- Soft P2 and wide split S2
- S4
- Prolong systolic murmur with late peaking
  - ✓ Mild PS→ short murmur ,peak earlier
  - ✓ Severe PS→ long murmur , peaking late
- Early ejection click close to the first heart sound
  - ✓ Mild PS→ ejection click is clearly separated from S1
  - ✓ Severe PS→ closer to S1 or not separable
- TR , Congestive Hepatopathy and edema

➢ Thrill is not a sign of severity in PS

What are the common syndromes associated with congenital PS ?

- Williams syndrome
- Noonan's syndrome
- Alagille syndrome
- Carcinoid syndrome (acquired condition)

Kindly see clinical features of mentioned syndrome from authentic books

How will you explain cyanosis in PS patient ?

Severe PS result in RVH and consequently raised RVSP . If there is underlying shunt like ASD or VSD then ↑RVSP will lead to shunt reversal and will cause to cyanosis .

How will you investigate this patient ?

After detail HX and examination , I would like to proceed with

- **CXR**

Scanned with CamScanner

- Diminished pulmonary vascular markings
- Prominent main pulmonary artery segment (post-stenotic dilatation)

- **ECG**
  - RAD , Right atrial hypertrophy →P pulmonale
  - Right ventricular strain
- **Echo**
  - To confirm the diagnosis
  - The assess the severity , determine the etiology and other valvular pathology
  - To assess RV dysfunction

How do you grade pulmonary stenosis?

- Mild → peak gradient < 36 mmHg (peak velocity <3m/s)
- Moderate PS→ peak gradient 36-64) (peak velocity 3-4 m/s)
- Severe PS→ peak gradient > 64 mmHg and (peak velocity > 4m/s)

Treatment

1. **Balloon Valvuloplasty**

Indications

- Symptomatic patient (mild and moderate PS)
- Asymptomatic severe PS

2. **Surgical repair**

It is indicated in symptomatic with moderate and severe PS patients who are either ineligible for or who failed balloon valvuloplasty

Scanned with CamScanner

IMPORTANT NEUROLOGY SHORT CASES

Contributed By: Dr Ayesha Zubair (Neurology Resident MH Islamabad)

Standard Neurological Examination

- Assess the gait of the patient. (Do not proceed with this step if you see any walking sticks or wheel chair near the patient.
- Assess higher mental functions
- Speech Assessment (Comprehension, fluency,articulation,repetition, reading ,writing and naming)
- Ask the patient if he can smell properly or not?
- Pupils- check both direct and consensual reactions.
- Test visual fields
- Fundoscopy
- Extra ocular movements
- Check facial sensation to light touch in all three divisions of trigeminal.
- Check for facial nerve palsy using phrases like show your teeth, screw your eyes
- Proceed for mouth examination , observe any wasting , fasciculation on tongue examine uvula for any Deviation.
- Test neck flexion making sure patient is not having any pain in neck before proceeding
- Now proceed for motor and sensory examination of upper limb : inspection observe for any signs of wasting fasciculation tremor. Observe outstretched hands with eyes closed to examine for pronation drift. Test tone at wrist and elbow. Test power (shoulder abduction, elbow flexion and extension, finger extension and abduction) test reflexes at biceps and triceps. Then check sensations in all dermatomes of upper limb and proceed to check for proprioception and vibration.
- Now proceed for lower limb motor and sensory examination : inspection : look for wasting, fasciculation tremor and hair loss. Check for any hammertoes, Charcot joints. Check tone, hip, and joints. Check power at hip, knee joints and assess foot dorsiflexion and plantar flexion. Check reflexes at knee and ankle. Check plantar and proceed for sensory examination test joint position sense in toes, vibration sense and light touch and pin prick,
- Lastly check coordination, test finger nose and heel shin test.

Scanned with CamScanner

Steps in the neurologic examination

In examining a patient, abnormalities of function lead to localization and, eventually, to the pathophysiology. These steps include the following:

I. General Appearance, including posture, motor activity, vital signs and perhaps meningeal signs if indicated.
II. Mini Mental Status Exam, including speech observation.
III. Cranial Nerves, I through XII.
IV. Motor System, including muscle atrophy, tone and power.
V. Sensory System, including vibration, position, pin prick, temperature, light touch and higher sensory functions.
VI. Reflexes, including deep tendon reflexes, clonus, Hoffman'sresponse and plantar reflex.
VII. Coordination, gait and Rhomberg's Test
Examining the comatose patient

Scanned with CamScanner

Assessment of Speech

Dysphasia/Aphasia:

Aphasia is the loss of ability to produce or understand language. This usually manifests as a difficulty speaking or understanding spoken language but reading and writing are also impacted.

In order to assess a patient with aphasia :

If the patient is unable to give history, ask from attendants. Before assessment, ensure the following

1. If the patient is right or left handed
2. If the patient is able to hear you
3. Education level

Then proceed for these four steps **(F C R N)**

1. **Check for fluency :**
   Ask simple question like what is your name? What is your address.
2. **Check for Comprehension :**
   When checking for compressive commands in 3 steps
   - **Command one:** Close your eyes
   - **Command two :** Pick up the paper and fold in half
   - **Command three :** Pick up the paper fold in half and then put in your pocket
3. **Repetition**
   Ask the patient to repeat a simple phrase like ' the sun in shining" and after that you may assess for complicated phrases.
4. **Naming**

Ask the patient to name familiar objects like watch , pen, and book.

When done with these the candidate may perform two other steps :

Check the ability to read and write.

Case presentation:

As per Command, I assessed the patient for speech difficulty. The patient had normal Comprehension, his speech was non-fluent and he was unable to repeat. The patient was having difficulties in finding words and was aware of his speech difficulty. The patient has brocas aphasia.

Classification of Aphasia

1. **Comprehension Intact**

If fluency is intact then there can be 3 situations :

Normal Patient:

- Patient can repeat after you

Scanned with CamScanner

- Patient can name objects

Anominal Aphasia:

- Patient can repeat after you
- But unable to name objects

Conductive Aphasia:

- Patient can -not repeat after you.

If fluency is not intact then there are 2 situations

Trans cortical Motor Aphasia:

- Patient can repeat after you.

Brocas Aphasia:

- Can- not repeat after you

2. **Comprehension Not Intact**:

Global Aphasia:

- Fluency not Intact

Trans cortical sensory aphasia:

- Fluency Intact
- Repetition Intact

Wernickes Aphasia

- Fluency Intact
- Can -not repeat after you

More about Aphasia:

Brocas Aphasia:

- Lesion affecting frontal lobe .
- Associated with right hemiparesis
- Impaired fluency, repetition
- Intact Comprehension

Wernickes Aphasia:

- Lesion in posterior superior temporal gyrus
- No motor deficit mostly but may have right superior visual field defect
- Comprehension not Intact
- Fluent but cannot repeat.

Conduction Aphasia:

- Lesion in architecture fasciculus
- Comprehension Intact, fluency normal
- Inability to repeat.

Trans cortical sensory aphasia:

- Lesion in post parietal occipital region.
- Comprehension not Intact, fluent but can -not repeat

Scanned with CamScanner

Trans cortical Motor Aphasia:

- Incomplete Lesion in brocas area
- Comprehension Intact, fluency not Intact
- Repetition Intact.

Nominal Aphasia:

- Lesion in angular gyrus
- Comprehension Intact fluency Intact, repetition Intact but naming difficulty.

Dysarthria :

Dysarthria is an impairment of motor functions necessary for speech production. When patient speaks listen for articulation errors, abnormalities of voice quality, irregularities of rate and rhythm

Types of Dysarthria :

1. **With normal rhythm :**

- Lesion may be lower motor neuron type:
  Flaccid , may occur due to weakness of soft palate or tongue or speech and may have a nasal quality e.g. MG, MND

2. **With abnormal rhythm :**

- Spastic dysarthria : UMN Lesion. Slurred and laboured speech e.g. pseudo bulbar palsy.
- Monotonous or extrapyramidal: speech is difficult to understand, soft mumbling without any change in tone e.g. Parkinson
- Ataxic: Scanning speech, disjointed rhythm, irregularity in Rhythm tone and volume of speech. MS, phenytoin toxicity , hereditary ataxia.

Dysphonia:

If the patient is able to talk but is unable to produce a normal volume of sound or speaks in a whisper this is dysphonia.

For assessment, ask the patient to cough and listen to quality of cough, say a sustained EEEEEE for fatiguability

Now if patient has normal cough vocal cords are okay so problem is laryngeal.

If patient has bovine cough then vocal cord paralysis

If patient says sustained EEEE and fatigues the myasthenia Gravis.

Scanned with CamScanner

GAIT

Gait: Gait is a complex and unique motor behaviour consisting of three primary components

1. Locomotion
2. Balance
3. Ability to adapt to environment.

Examination :

Keys aspects of gait examination include

1. Assessment of lower limbs
2. Examine postural control
   Pull test: Standing in the back of the patient and exerting a sudden tug on the shoulder and watching for a corrective step backward.
3. Observe walking
4. Additional Maneuver :

Rhombergs test , tandem walking , walking on heels to assess foot drop, walking on toes to assess weakness of gastrocenemius.

TYPES OF GAIT:

Symmetrical Gait:

Small paced

Normal paced.

In case of small paced gait:

Observe the posture if stooped and having decreased arm swing patient is likely having Parkinson's disease.

If posture normal and normal arm swing he may be having stroke.

In case of normal paced gait:

Observe feet separation:

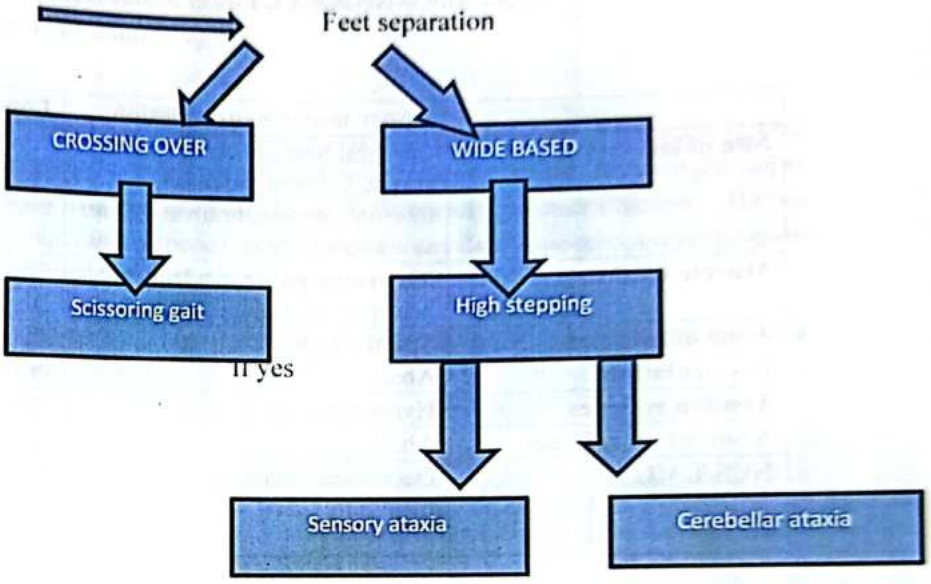
If patient has crossing over then he has scissoring gait.

If patient has wide based gait with high stepping he has sensory ataxia

and if no high stepping then he has cerebellar ataxia.

Scanned with CamScanner

Normal Paced Gait



If feet separation neither crossing over nor wide based then:
Observe for the following :

1. If high stepping then most probable diagnosis is bilateral foot drop
2. If pelvis rotating then waddling gait.
3. If disjointed movements then apraxic gait.
4. If bizzare gait then conside functional or conversion Disorders.

Asymmetrical Gait:

- Look for the following :
- Is the patient in pain?
- Look for bony deformity ?
- Does one leg swing out to side, hemiplegic gait?
- Look at the knee length.

Differentials of Gait:

- **Small paced:** Parkinsonian gait, basal ganglia dysfunction
- **Scissoring gait:** Spastic paraparesis, CP, MS , cord compression
- **Sensory ataxia:** indicates loss of joint position sense Romberg will be postoperative e.g. peripheral neuropathy, post column loss.
- **Cerebellar ataxia:** veers or falls towards lesion e.g. phenytoin toxicity , alcohol, MS
- **Waddling gait:** Myopathies, Becker muscular dystrophy
- **Apraxic gait:** Mostly frontal lobe Lesions e.g. NPH, CVA

Scanned with CamScanner

- **Hemiplegia:** unilateral UMN stroke, MS

Upper Motor Neuron Vs. Lower Motor Neuron

	Upper motor neuron lesion	Lower motor neuron lesion
Site of lesion	Cerebral hemisphere includes cortex, Corona radiation, internal capsule, brain stem and spinal cord	Ant horn cells, nerve roots, peripheral nerve, neuromuscular junction
Muscle weakness	May cause either quadriplegic, hemiplegia, diplegia, paraplegia	Proximal (myopathy) Distal (neuropathy)
Tone of muscles	Spastic, rigid	Hypotonia
Fasciculation	Absent	Present particular tongue
Tendon reflexes	Hyper reflexia	Hyporeflexia
Abdominal reflexes	Absent	Present
NCS/EMG	Decreased interference and firing rate	Abnormal nerve conduction, large motor units, fasciculation and fibrillation

Scanned with CamScanner

STROKE

Lesion: Upper motor neuron at the levels of cerebral hemisphere,
Upper motor neuron at the level of brain stem.

Case:

As per Command, I have done the motor examination of this gentle man lying comfortably in bed. On Examination, he has increased Tone, Hyper reflexia and Decreased power in his right upper and lower limb. His power is 2/5 in upper and 3/5 in lower limb. He has extensor Planters. He has circumducting or hemiplegic gait. On his speech examination he has fluent speech Comprehension is not Intact and repetition is poor therefore he has sensory aphasia .

According to my examination, the patient has upper motor neuron lesion with aphasia my top most differential would be stroke with aphasia.

Differentials Of Stroke:

- Transient ischemic attack
- Space occupying lesion in brain
- Hemiplegic migraine
- Todd's paralysis
- Hypoglycemia
- Conversion disorder.

Stroke is further divided into:
Ischemic or Hemorrhagic stroke.

Ischemic Stroke

Toast Classification Of Stroke:

1. Large artery atherosclerosis
2. Cardioembolic
3. Small vessel diseases, penetrating artery , lacunar infarcts
4. Stroke of other determined cause(Vasculitis, CADASIL, CARASIL)
5. Stroke of undetermined cause (More than 2 potential causes of stroke.

Also, learn Bamford classification of stroke as well

Investigations

1. CT scan brain to rule out hemorrhage
2. CTA head and neck and CT Perfusion
3. BSR, HBA1C, Lipid profile
4. ECG, 2D echo
5. 24hrs Holter monitoring
6. Most diagnostic for stroke: MRI DWI and ADC

Scanned with CamScanner

Territories of stroke with signs and symptoms

Vascular territory	Signs and symptoms
RT Middle cerebral Artery	Weakness on Left side of the body associated with hemi spatial neglect May have gaze preference to the right
Left middle cerebral Artery	Weakness on RT side of the body Aphasia Left gaze preferences
Anterior cerebral Artery infarct	Motor and sensory deficit more in lower limbs as compared to upper limbs Primitive reflexes Gait apraxia
Unilateral post cerebral artery	Homonymous hemianopia with macular sparing Homonymous hemianopia and alexia without agraphia
Bilateral Post cerebral artery	Cortical blindness Bilateral cortical blindness with normal Ophthalmology Anton syndrome: cortical blindness with denial of blindness and confabulation.

Management

1. Window Period

(0 To 4.5 Hours)

If Patient Presents Before 4.5 Hours Of Stroke Onset Patient Is Said To Be In Window Period Of Thrombolysis.

2. **Thrombolysis**

If Patient Is In Window Period Rule Out Contraindication Of IV TPA (Alteplase) Inj Alteplase Is Given As 0.9mg/Kg Over 1 Hour While Close GCS And BP Monitoring.

Pre Requisite For TPA:

- NIHSS >5
- NIHSS <5 But Disabling Stroke I.E. Hemianopia, Severe Dysarthria, Rt Sided Weakness
- ASPECT Score More Than 5
- BP Target<180/110
- No History Of Ischemic Or Hemorrhagic Stroke In Last 3 Months
- No Anti-Coagulant In Past 24 Hours

3. **Out of thrombolysis window:**

Assess patients NIHSS score if more than 6, ASPECT score more than 6 and patients stroke is less than 24 hours ago then get CT angiography and CT Perfusion to see any large vessel occlusion and ischemic penumbra, if found patient is candidate for Thrombectomy.

4. **Medical Management :**

- Tab disprin 300mg OD if NIHSS >5 and dual anti-platelet if NIHSS<5

Scanned with CamScanner

- Statins
- Optimal management of hypertension and diabetes
- Anticoagulation for Cardioembolic stroke
- Carotid stenting if carotid stenting significant
- Swallowing assessment
- Pass NG, Foley catheter
- Daily limb physio for Rehab.

Hemorrhagic Stroke:

Causes:

- Capsuloganglionic bleed may be due to hypertension
- Lobar bleed secondary to DVST
- Sub arachnoid hemorrhage secondary to aneurysm
- Cerebral amyloid angiography
- AV malformation
- Moya Moya disease
- Primary or metastatic tumour like melanoma, choriocarcinoma, lung, renal thyroid.

Investigations

- CT brain plain
- CTA head or CTV
- MRI Brain
- Digital subtraction angiography

Management

1. **Hypertensive bleed:**

- Mostly in basal ganglia or brain stem location
- Keep BP target less than 140/90
- Monitor for seizures, prophylactic use of anti epileptvs is not recommended.
- Monitor for any midline shift. If patient develops sign and symptoms of midline shift give information Mannion, hypertonic saline or steroids, if still persistent effect then Neurosurgery consult for decompression craniectomy.
- Limb physio
- Swallowing assessment
- Bowel and bladder care.

2. **Bleed due to DVST:**

- Is usually detected on CTV head
- Start DOACs in therapeutic dose
- Give anti-epileptics if seizures

3. **Subarachnoid hemorrhage :**

- CTA head for evaluation of aneurysm

Scanned with CamScanner

- In case of any aneurysm, Coiling is the treatment of choice.
- Give tab nimodipine 60mg 4 hours for 21 days to prevent any vasospasm.
- Physiotherapy
- Bladder and bowel care.

Scanned with CamScanner

MULTIPLE SCLEROSIS

Lesion:

UMN paraparesis + dorsal column
UMN paraparesis+ cerebellum
UMN Paraparesis + cerebellum + dorsal column
UMN paraparesis + cerebellum + dorsal column + peripheral neuropathy

Case: If Command to examine eyes

As per Command, I have examined this patient. On examination, the patient has dissociation conjugate movement of eyes. There is nystagmus on abducting eye, when the abducting eye is covered abduction of the opposite eye is normal. There is nystagmus on looking at both sides. The right pupil exhibits a loss of direct light reflex, whereas the consensual light reflex is preserved. The right optic Disc is pale and has distinct margins. The patient has internuclear opthalmoplegia, relative affluent pupillary defect and optic atrophy. My top most differential diagnosis is demyelinating brain disease.

Differential Diagnosis:

1. **Idiopathic CNS demyelinating disease**
   - Multiple Sclerosis
   - ADEM
   - NMOSD
2. **Infections:**
   - Lyme disease
   - Syphilis
   - HIV serology.
3. **Vascular:**
   - Stroke
   - Leukoariosis
   - Susac disease
4. **Hereditary;**
   - Adereoleukodystrophy
   - Metachromatic leukodystrophy
   - CADASIL
   - Fabrys disease
   - Alexander's disease
5. **Nutritional:**
   - Vitamin B12 deficiency
6. **Autoimmune**
   - SLE

Scanned with CamScanner

- Antiphospholipid syndrome
- Sjögren's disease

7. **Malignancy :**
    - CNS Lymphoma
    - Paraneoplastic etiology

Symptoms of MS:

- Sensory disturbances
- Weakness
- Optic neuritis
- Ataxia
- Diplopia
- Vertigo
- Fatigue
- Dysarthria
- Dysphagia

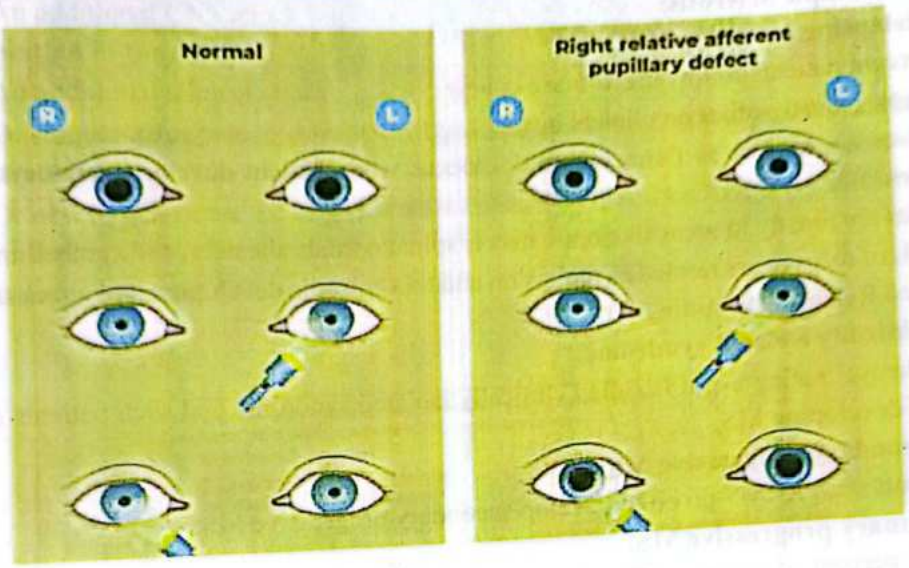
Important Signs Of MS:

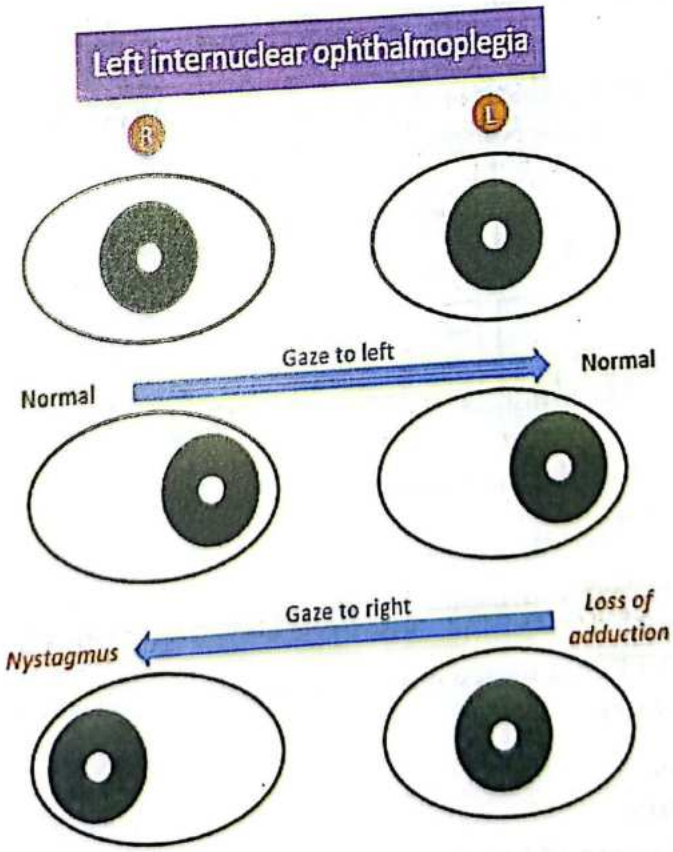
- Internuclear opthalmoplegia
- Hypermedia saccades
- RAPD
- Lehermitte sign
- Staccato speech
- Intention tremor
- Past pointing
- Rebound phenomenon

Lehermitte sign other causes

1. Multiple sclerosis
2. Cervical myelopathy
3. Cervical cord tumour
4. Subacute combined degeneration of cord.

Scanned with CamScanner





Scanned with CamScanner

Types Of Multiple Sclerosis:

1. **Relapsing remitting MS:**

- 85 percent patients follow this disease course
- Diagnosis mostly relies on clinical history
- Relapses are known as flares or attacks, occur when patient develop symptoms causes by plaques.
- Plaques are mostly in areas like optic nerve, spinal cord, brain stem, and cerebellum.
- Periods of recover are termed as remission and this episodic development of attack and recover is called Relapsing remitting.

2. **Clinically isolated syndrome:**

- First demyelinating event is called clinically isolated syndrome and such patients are at high risk of developing MS,

3. **Secondary progressive MS:**

Most patients with RRMS go on to develop secondary progressive MS.

4. **Primary progressive MS:**

Almost 10 percent of the patients have a disease course that is progressive from onset without Relapses or remission termed as PPMS.

Diagnosis:

1. MRI brain: Typically, multiple areas of abnormal signal intensity are present on T2 weighted brain imaging. These are ovoid in appearance and are located in

- Corpus callous
- Periventricular
- Juxtacortical
- Deep white matter
- Subcortical white matter.

Periventricular plaques give rise to distinct appearance of Lesions called Dawson fingers.

2. MRI Spine:

Plaques can be seen oriented longitudinally along the cord often with posterior location spanning one or two vertebral segments.

3. CSF Analysis:

Shows normal glucose, lymphocytosis, normal or slightly elevated protein and oliogoclonal bands.

4. Visual evoked potentials:

Characteristic findings of VEPs that suggest demyelination include asymmetric delay of the P100 potential and conduction blocks

Diagnostic Criteria of MS

Dissemination in Space DIS

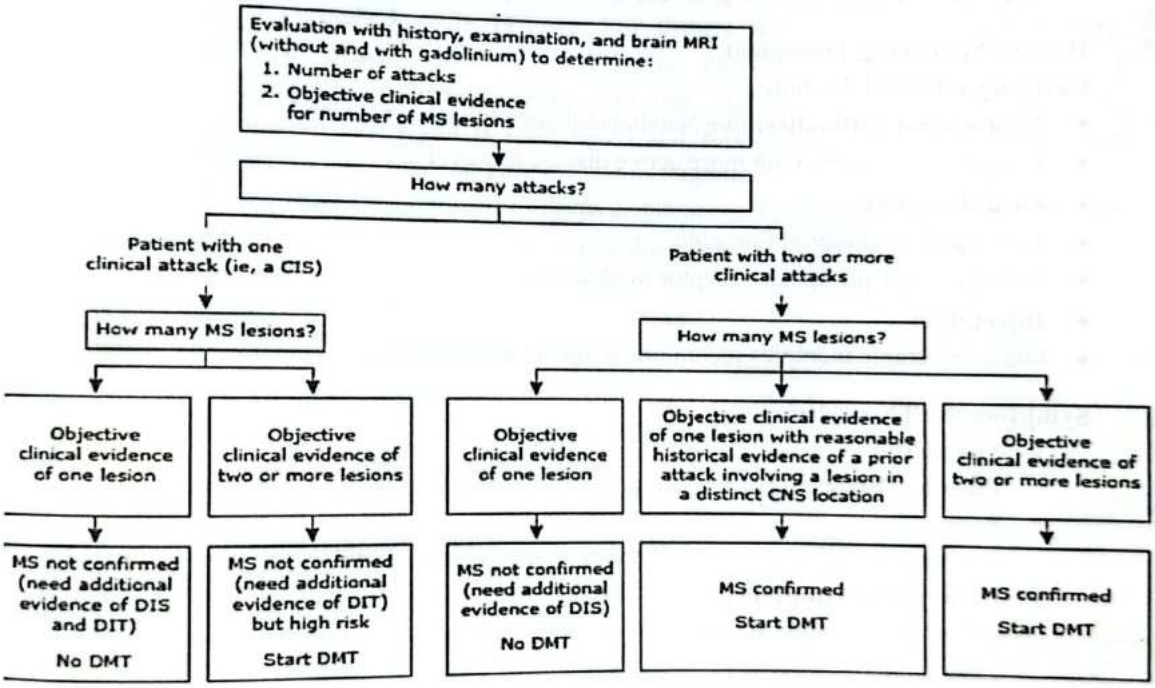
- One or more hyperintense T2 Lesions on MRI that Characteristic of MS in at least two of four MS typical regions.

Scanned with CamScanner

- An additional CNS attack implicating a different CNS site.

Dissemination in time DIT:

- An additional clinical attack
- Or simultaneous presence on MRI of gadolinium enhancing and non-enhancing Lesions at any time.
- Or new hyperintense T2 or gadolinium enhancing lesion on follow up MRI irrespective of its timing with reference to baseline.
- Demonstration of CSF specific OCBs


Evaluation with history, examination, and brain MRI (without and with gadolinium) to determine:
1. Number of attacks
2. Objective clinical evidence for number of MS lesions
How many attacks?
Patient with one clinical attack (ie, a CIS)
Patient with two or more clinical attacks
How many MS lesions?
How many MS lesions?
Objective clinical evidence of one lesion
Objective clinical evidence of two or more lesions
Objective clinical evidence of one lesion
Objective clinical evidence of one lesion with reasonable historical evidence of a prior attack involving a lesion in a distinct CNS location
Objective clinical evidence of two or more lesions
MS not confirmed (need additional evidence of DIS and DIT)
No DMT
MS not confirmed (need additional evidence of DIT) but high risk
Start DMT
MS not confirmed (need additional evidence of DIS)
No DMT
MS confirmed
Start DMT
MS confirmed
Start DMT

Other causes of CSF oliogoclonal bands:

- Neurosacroidosis
- Neurosyphilis
- CNS Lymphoma
- NMO
- ADEM
- Behcets disease

TREATMENT MODALITIES

Scanned with CamScanner

Acute attacks:

Indication for acute treatment:

Functionally disabling symptoms with objective evidence of neurological impairment such as loss of vision, diplopia, weakness or cerebellar symptoms.

1. Initial therapy with glucocorticoid

- Iv methylprednisolone 500mg to 1000mg for 3 to 7 days
- Or oral prednisone 1250 mg daily

2. Plasma exchange:

- Use for patients with acute severe neurological deficits caused by MS attacks who have poor response to treatment with glucocorticoid. Daily or every other day for total 3 to 7 treatment.

Disease Modifying Treatment:

Category Of DMT Include

- **Monoclonal antibodies:** like Natalizumab, ocrelizuman, rituximab
- Preferred in patients with more active disease however high risk for infection
- **Oral therapies:**
- Fumarate I.e. dimethyl fumarate
- Sphingosine 1 phosphate receptor modulators
- **Injectable:**
- Older injectable therapies recombinant human interferon beta 1b

Symptomatic Therapies:

1. **Spasticity:**
   Baclofen 10mg TID or tinzanidine 2mg three times is usually prescribed.
2. **Pain:**
   Neuropathic pain of MS usually does not respond to NSAIDs, gabapentin, carbamazepine
3. **Paroxysmal symptoms :**
   Lehermitte symptoms and tonic symptoms respond to Treatment with carbamazepine, gabapentin.
4. **Bladder dysfunction :**
   Anti-cholinergic agents like oxybutynin, tolterodine
   Mirabegron
   Intermittent self-catheterization.

Other Imp points:

NMOSD (Devics disease)

Aggressive inflammatory disorder characterised by recurrent attacks of optic neuritis, transverse myelitis, or intractable nausea and vomiting. Anti- aquamarines 4 abs is present in majority of patients. Treatment include IV steroid and Immunosuppressive therapies.

Scanned with CamScanner

ADEM (Acute demyelinating encephalopathy)
Monophasic demyelinating disease of young/ children. Mostly post infectious.
MRI brain. Shows wide spread extensive Lesions.
Treatment: IVMP and plex

Friedrich Ataxia

Lesion: UMN+ Cerebellar signs+ dorsal column signs

CASE:

As per Command, I have examined the patient on inspection the patient has pes cavus, kyphoscoliosis, and high arched palate. In lower limbs, there is distal weakness and wasting. Lower limb reflexes are absent with extensor Planters. There is bilateral limb ataxia with dysdiadochinesia, past poiting, impaired heel shin test. Patient's vibration sensation and proprioception are impaired. His gait is wide based and ataxic. Rhomebrtest is positive. On Examination of his eyes, he has bilateral gaze evoked nystagmus.
Keeping in view his cerebellar symptoms, pes cavus and depressed reflexes with extensor Planters and peripheral neuropathy. My top most differential diagnosis is Friedrichs Ataxia.

Differential Diagnosis:

- Ataxic telengiectasia
- Abetalipoproteinemia
- Ataxia with Vit E deficiency
- Refsums disease

Differential Diagnosis Of Depressed Ankle Jerks

With Extensor Plantars:

1. Subacute combined degeneration of cord
2. Tabes dorsalis
3. Friedrich ataxia
4. Motor neuron disease.

Features of Friedrich Ataxia :

1. Pes cavus
2. Kyphoscoliosis
3. High arched palate
4. Gait ataxia
5. Cerebellar nystagmus
6. Wasting and weakness of lower limbs
7. Depressed tendon reflexes
8. Cerebellar ataxia
9. Some other features :
    - Diabetes
    - Optic atrophy

Scanned with CamScanner

- Hypertrophic cardiomyopathy
- Sensorineural deafness

Investigations :

1. Complete blood count, HBA1c, fasting blood sugar
2. ECG, 2D Echo
3. NCS/EMG
4. MRI brain shows atrophy of spinal cord and medulla
5. Genetic testing for triplet repeat expansion

Treatment :

1. Occupational and physical therapy programme should initiate early and modified over time.
2. Yearly cardiac evaluation for evidence of arrhythmias and cardiomyopathy.
3. Scoliosis screening annually
4. Ophthalmology and audiology evaluation
5. Annual screening for Diabetes.
6. Newer drugs approved :

Spastic Paraparesis

Lesion:

UMN paraparesis with normal sensation
UMN paraparesis with sensory loss
UMN paraparesis + Dorsal column signs

Case:

As per Command, I have examined this patient. On inspection, there were no evidence wasting, scars or fasciculation's. The tone was increased in bilateral lower limbs with hyper reflexia and extensor Planters. Ankle clones was present. Sensation in lower limb was impaired with sensory level upto umbilicus. There was altered proprioception. The patient has Spastic paraparesis due to lesion at T10 level of spinal cord.

Scanned with CamScanner

Differential Diagnosis

UMN Paraparesis with normal sensation :

- Parasaggital meningioma
- Hereditary Spastic paraplegia
- Primary lateral sclerosis
- Superior saggital sinus thrombosis
- Bilateral stroke
- HTLV1
- Cerebral palsy
- Syringomyelia

UMN paraparesis with sensory level(see compressive and non-compressive causes below) :

- Potts disease
- Dural AVF
- Meningioma
- Transverse myelitis

UMN paraparesis + Dorsal column(C-MAST) :

- Cervical myelopathy
- Multiple sclerosis
- Friedrich ataxia
- Subacute combined degeneration
- Tab paresis

UMN + ebellum

- MS
- Friedrich's ataxia
- Spino-cerebellar degeneration

UMN +Dorsal column+ cerebellum

- MS
- FA

UMN + with depressed ankle (P+C.S and MAST)

- Peripheral neuropathy + cervical myelopathy
- Peripheral neuropathy + bilateral stroke
- MND
- FA
- SACD (↓B12)
- Tabo-paresis

UMN +cerebellum + Dorsal column

- MS
- FA

UMN +cerebellum +dorsal column+ peripheral neuropathy

- FA

Scanned with CamScanner

- SACD(↓B12)

Clinical Findings In Spinal Cord Disorder:

Sensory Abnormalities :

- Local pain
- Radicular pain
- Funicular pain
- Hyperesthesia
- Lehermitte phenomenon
- Loss of joint position sense below level of lesion
- Loss of sensation at or below lesion.

Motor abnormalities :

Upper motor neuron :

Hypertonia
Hyper reflexes
Gait abnormalities

Lower motor neuron

Atrophy
fasciculation's
Hypotonia
Hyporeflexia

Compressive Myelopathy :

UMN + Sensory Loss

1. **Extra Dural Cord Compression :**
   Severe Backache Followed By Lower Limb Weakness And Then Sphincteric Involvement.
   Most Common: Tb Spine
2. **Intradural Cord Compression :**
   Mild backache followed by weakness of both lower limb and then sphincter involvement
   Example: Meningioma and Dural AVF
3. **Intramedullary Cord Compression :**
   First involves sphincter then bilateral lower limb weakness which may or may not be associated with backache
   Example: Transverse myelitis, Anterior spinal artery thrombosis.

If UMN with quadriparesis:

Lesions sill be in cervical cord
Deep tendon reflexes will be decreased in upper limbs and upper motor neuron signs will be found in lower limb then the lesion is at C5 or below
If
Deep tendon reflexes are increased n upper limb and upper motor neuron signs in lower limbs the lesion is at C4 or above.

Scanned with CamScanner

UMN paraparesis + Normal sensation

1. **Hereditary Spastic paraparesis or Stumpell-lorrain syndrome:**
   - May be X linked, Autosomal dominant or recessive.
   - Characterized by severe Spasticity in lower limbs.
   - May have sensory impairment
   - Diminished proprioception and vibration
   - Pes cavus may be seen.
2. **Tropical Spastic Paraparesis**
   - Known as HTLV1 associated myelopathy
   - Characterized by progressive Spastic paraparesis
   - Usually due to HTLV1 virus

Other important spinal cord lesions:

Cauda Equina: LMN paraparesis with up going plantars

Lesions of cauda equina may result in one of the following signs and symptoms of lower limbs:

- Radicular pain
- Bladder and bowl dysfunction (usually late onset)
- Impotence
- Asymmetric Saddle anesthesia
- Asymmetric Flaccid paraplegia
- Absent tendon reflexes.

Conus Medullaris: LMN paraparesis with down going plantars

- Commonly acute and Symmetrical
- Early onset bowel and bladder dysfunction
- Impotence
- Symmetrical saddle anesthesia.

Investigations :

1. MRI brain and spine with and without contrast to identify structural and demyelinating Lesions
2. MRA of spinal cord to look for dural AVF
3. CSF RE to rule out chronic infections and demyelinating Lesions
4. NCS/EMG
5. Antibodies to HTLV 1
6. HIV serology
7. Genetic testing for HSP

Treatment :

- Potts disease ---- surgical intervention
- Dural AVF------ embolization of AVF

Scanned with CamScanner

- Transverse myelitis -----High dose corticosteroid and plasma exchange
- Hereditary Spastic paraparesis ---- genetic counselling
- HTLV1 Tropical Spastic paraparesis ---- high dose corticosteroid
- Conus medullaris/ Cauda equina---- Emergent decompression is recommended other mode of treatment is radiotherapy.
- Supportive measures like physiotherapy and exercise
- Baclofen to reduce Spasticity
- Prophylactic anticoagulant
- Sildenafil for erectile dysfunction

Scanned with CamScanner

MOVEMENT DISORDERS AND PARKINSON'S DISEASE

Case:

As per Command, I have examined the patient. The patient has mask like expression less face low volume monotonous speech. There is a continuous slow pill-rolling tremor of the hands. There is rigidity in the arms. There is bradykinesia. On gait examination patient has stooped posture and reduced arm swing. There is postural instability with propulsion and retropulsion. My top most differentials is that the patient has Parkinson's disease.

Diagnostic Criteria For Parkinson's ;

1. **Clinical features :**
    - Resting tremors
    - Bradykinesia
    - Rigidity
    - Loss of postural reflexes
    - Flexed posture
    - Motor block

Definite PD:

At least 2 features must be present with one being bradykinesia.

Probable PD:

When only Bradykinesia or resting tremor is present.

Possible PD:

When two features are present but neither resting tremor nor bradykinesia.

Differential Diagnosis :

1. Essential Tremors
2. Dementia with lewy body
3. Multiple system atrophy
4. Cortico-basal degeneration
5. Progressive supranuclear palsy

Parkinson's disease	Essential tremors
Occurs at rest	Occurs on movements
Mostly unilateral	Bilateral action Tremors of hand and fore arm
With rigidity, bradykinesia and gait instability	With or without tremor in other location like head , voice or lower limbs
No family history	Positive family history
Is treated with levidopa	Is treated with propranolol 60 to 80mg OD or primidone 25mg

Scanned with CamScanner

Lewy Body Dementia :

Dementia with lewy bodies is one of the most common type of Dementia secondary to Alzheimer's disease. Patients have Dementia, visual hallucinations, Parkinsonism, cognitive fluctuations, dysautonomianand sleep disorders.

Cortico-basal Degeneration :

Characterised by frontoparietal cortical atrophy in addition to degeneration in extra pyramidal system

Present with limb apraxia, cortical sensory loss, and alien limb phenomenon

Myoclonus can also occur and Dementia may occur.

Progressive supranuclear palsy :

- Most common Parkinson plus syndrome
- Manifest as abnormal vertical then horizontal saccades
- Patient may have difficulty in open eyes, swallowing, prominent falls, may have depression and apathy
- Parkinsonian features are Symmetrical, axial rigidity is more prominent then limbs.
- Poor response to levodopa.

Multi system Atrophy:

- Olivopontocerebellar atrophy
- Parkinsonism, Autonomic failure, cerebellar dysfunction, pyramidal signs
- MSA-P when Parkinsonian features are prominent
- MSA-C when cerebellar features are prominent.
- When Autonomic is more it is called Shy dragger syndrome.

Investigations :

Mostly clinical diagnosis

In early onset:

Serum copper levels, serum ceruloplasmin levels, 24 hours urinary copper, KF rings, USB Abd, LFTs ,Serum ferritin.

MRI brain to rule out Huntington and NBIA.

In late onset :

MRI Brain

SPECT/PET scan

MIBG scan.

IMP IMAGING FINDINGS:

MSA-C : cerebellar atrophy , hot cross bun sign

MSA-P : Bright Putaminal ring sign

PSP: Middle brain atrophy

NBIA: Eye of the tiger sign.

PD : Normal

Wilson: hyper intensity in bilateral globes pallidus

Scanned with CamScanner

TREATMENT:

Pharmacotherapy:

Dopaminergic Agents:

1. Dopamine precursor e.g, levodopa with carbidopa
2. Dopamine agonist e.g, bromocriptine , ronirole, amantadine, apomorphine.
3. COMT inhibiter e.g. Entacapone, Tolcapone
4. MAO B inhibitor e.g, selegeline

Non -Dopaminergic Agents:

- Anticholinergic agents like Trihexyphenidyl or amitriptyline
- Antiglutaminergic e.g Amantadine
- GABAnergic e.g, Lorazepam, Clonazepam

Atypical neuroleptics:

Serotonin and Dopamine antagonist e.g, Quietapine.

Surgical Options:

1. Deep brain stimulation

   Some symptoms that respond to DBS are tremors, rigidity, bradykinesia, dystopia and dyskinesias.

   Symptoms that do not respond are gait freezing , postural instability, hypophonia, and dementia.

Hypokinetic Movement Disorders:

Includes the following :

1. Akinesia or bradykinesia: Parkinson's disease
2. Apraxia i.e. inability to execute coordinated work or actions e.g. parietal lobe Lesions.
3. Tics e.g Tourette syndrome
4. Catatonia e.g schizophrenia
5. Stiff ms eg Stiff person syndrome

Hyperkinetic Movement Disorders :

Includes the following :

1. Akathisia
2. Ataxia
3. Athetosis
4. Chores
5. Hemiballismus
6. Dystopia
7. Essential tremors

Huntington Chorea:

Inherited Progressive Neurodegenerative Disorders. Characterized By Choreiform Movements, Psychiatric Problems And Dementia.

Symptoms

Scanned with CamScanner

- **Motor symptoms :**
  Chores, dystonia, Dysphagia, gait impairment
- **Psychiatric symptoms :**
  Apathy, irritability and depression.
- **Cognitive impairment :**
  Loss of insight.

Investigations :

1.Genetic testing

2. MRI brain

Treatment

- **First line:**
  VMAT Inhibitors I.e. tetrabenazine
- Second line:
  Anti-psychotic I.e. risperidone, olanzapine
  Physical and Occupational therapy.

Scanned with CamScanner

ATAXIA AND CEREBELLAR SYNDROMES

Sensory Ataxia
Vestibular Ataxia
Cerebellar Ataxia

CASE

Nystagmus :

As per Command, I have examined the patients' eyes. On examination, the patient's ey demonstrated a horizontal Nystagmus with fast component to the left. The Nystagmus increases Left gaze I.e, unidirectional. The Nystagmus is suppressed by visual fixation and adapts continued gaze. My topmost differential diagnosis is that the patient has vestibular Nystagmu with right side peripheral vestibular lesion.

Motor examination :

As per Command, I have done the motor examination. On Examination he has decreased tone i his lower limb, power is 5/5 reflexes are normal, there is impairment of heel shin test, patient ha truncal Ataxia, wide based gait on further examination the patient also had scanning speech an past pointing and dysdiadochinesia. My top most differential is that patient has a cerebell lesion.

ATAXIA:

It is the inability to make smooth, accurate and co-ordinated movements. It is a symptom not specific disease or diagnosis. Ataxia is most often used to describe walking that is uncontrolle and unsteady but Ataxia can affect gait, trunk, limb , speech and eye movements.

Ataxia can arise from the following disorders :

1. Cerebellum (most common)
2. Sensory pathways (post column, dorsal root ganglion)
3. Frontal lobe Lesions via frontocerebellar fibers.
4. Extrapyramidal system
5. Vestibular system.

	Cerebellar ataxia	Sensory ataxia
Fall	Less common	Do occurs
Postural instability	++	++
Stance	Wide based	Wide based
Trunk posture	Leaning forward	Stooped
Gait initiation	Normal	Normal
Steps	Staggering	High steppage
Tandem gait	Unable	Variable
Rhombergs	Can- not stand with feet closed	Can stand with feet close together but when eyes close imbalance occurs
Heel shin test	Not possible	Normal
Associated features	Dysmetria, dyssnergia, rebound Phenomenon, dysarthria, jerk nystagmus	Decreased joint position and vibration sense. Depressed ankle jerks

Scanned with CamScanner

Cerebellar Ataxia:

CAUSES:

1.Developmental:

- Arnold chiari malformation
- Dandy walker malformation

2.Hereditary :

- Spinocerebellar ataxia
- Friedrich ataxia

3.Vascular:

- Ischemic cerebellar stroke
- Cerebellar hemorrhage
- AV malformation

4.Toxin associated :

- Alcohol
- Metals (lead, mercury)

5.Medication Associated :

- Anti convulsants
- Amiodarone
- Cytotoxic drugs

6.Neoplastic

- Metastatic I.e lungs, breast, melanoma and renal CA
- CP angle tumour
- Hemangioblastoma

7.Infections

- Abscess
- Acute viral cerebellitis
- HIV encephalitis
- Prion disease

8. Immune Associated :

- Multiple sclerosis
- Gluten ataxia
- Paraneoplastic

9. Metabolic:

- Hypothyroidism
- Hypoglycaemia
- Deficiency in B1, B2 or E

Signs of cerebellar disease:

1. **Truncal Ataxia**

Oscillation while sitting or standing. Falling may occur towards. Side of unilateral Lesions.

Scanned with CamScanner

2. **Wide based gait**

Feet placed widely apart ,difficulty standing with feet together.

3. **Dysdiadochinesia :**

Impaired rapid alternating movement.

Tested by alternating supination and pronation of hands

4. **Dysmetria:**

Errors in judging distance with body movements, tested by finger nose tests

5. **Kinetic tremor:**

Tremor that occurs with voluntary movements with worsening on target approach.

6. **Scanning speech:**

Abnormally long pauses.

7. **Dysarthria :**

Unclear pronunciation

8. **Hypotonia:**

Decreased muscle tone.

9. **Dysmteric Saccades**

Analogous to limb dysmetria, resulting in Hypermedia or hypometria , on saccade to a target presented.

10.**Nystagmus**

Inability to maintain gaze fixation with slow phase followed by rapid saccadic correction. Commonly gaze evoked but also in primary position.

Peripheral Vertigo VS Central Vertigo:

	Peripheral vertigo	Central vertigo
Imbalances	Mild	Severe
Nystagmus	Unidirectional Inhibited by fixation	Bidirectional not inhibited by fixation
Nausea	Severe	Variable
Neurological symptoms	Rare	Common
Head thrust test	Positive	Negative
Location of lesion	Labyrinthine	Cerebellum, brain stem

Scanned with CamScanner

Peripheral Nystagmus Vs Central Nystagmus

	Peripheral	Central
Direction	Unidirectional	Bidirectional or unidirectional
Purely horizontal without rotatory component	Uncommon	Common
Vertical nystagmus	Never	May be
Visual fixation	Inhibits nystagmus and Vertigo	May be present
Tinnitus	Often present	Rarely
Vertigo	Severe	Mild
Duration	Short but recurrent	May be chronic
Examples	Meniere disease Vestibular neuronitis	Vascular etiology, or demyelinating

Investigations :

- Peripheral blood smear
- Electrolytes
- RFTS, LFTs
- Thyroid function test, VDRL, TPHA
- MRI brain
- MRI cervicovertberal junction
- B12 folate levels, vit E levels
- Autoimmune work up ANA, ANCA
- Ace levels
- Anti Gliaden abs
- Anti-HI, Anti YO, Anti-Ri
- CSF R/E

Treatment

1. For cerebellar stroke follow guidelines of ischemic stroke
2. For cerebellar haemorrhage if haemorrhage more than 3cm then it requires surgical evacuation
3. Toxins and nutrition deficiency, treatment of Wernicke's Korsakoff disease
4. Paraneoplastic origin, identity underlying neoplasm
5. Gluten associated ataxia, follow gluten free diet , IVIG or mycophenolate mofetil, cyclosporine
6. Infections like CJD, treatment of CJD
7. Spinocerebellar atrophy, conservative management like drugs for Parkinson's, seizure

MRI FINDINGS IN DIFFERENT ATAXIAS:

1. **Isolated cerebellar atrophy:**

Scanned with CamScanner

SCA, celiac disease, Paraneoplastic, ataxic telengiectasia

2. **Cerebral and cerebellar atrophy:**
   Other types of SCA, mitochondrial cytopathy
3. **Normal cerebellum but atrophic cord:**
   Friedrich ataxia
4. **Cerebellar tonsilar herniation :**
   Craniovertebral junction Anamoly
5. **Hot cross bun sign(posting and cerebellar atrophy):**
   MSA
6. **Molar tooth sign:**
   Joubart sign
7. **B/L mammillary body hyper intensity:**
   Wernickes encephalopathy
8. **T2 flair hyperintense signal in bilateral pulmonary of thalamus(pulvinar)**
   Variant CJD
9. **T2 Flair caudate and putamen (hockey stick)**
   Sporadic CJD.

Scanned with CamScanner

BRAIN STEM SYNDROME

Case:

As per Command, I have examined the patients cranial nerves. On Examination, he has a right sided Horner syndrome, horizontal nystagmus with fast component to the right, right sided facial numbness, and right sided palatial paralysis with Absent gag reflex. The patient has dysarthria. On further examination patient, had right sided cerebellar signs and left sided impairment of pain and temperature sensation. As per my examination findings patient has lateral medullary syndrome.

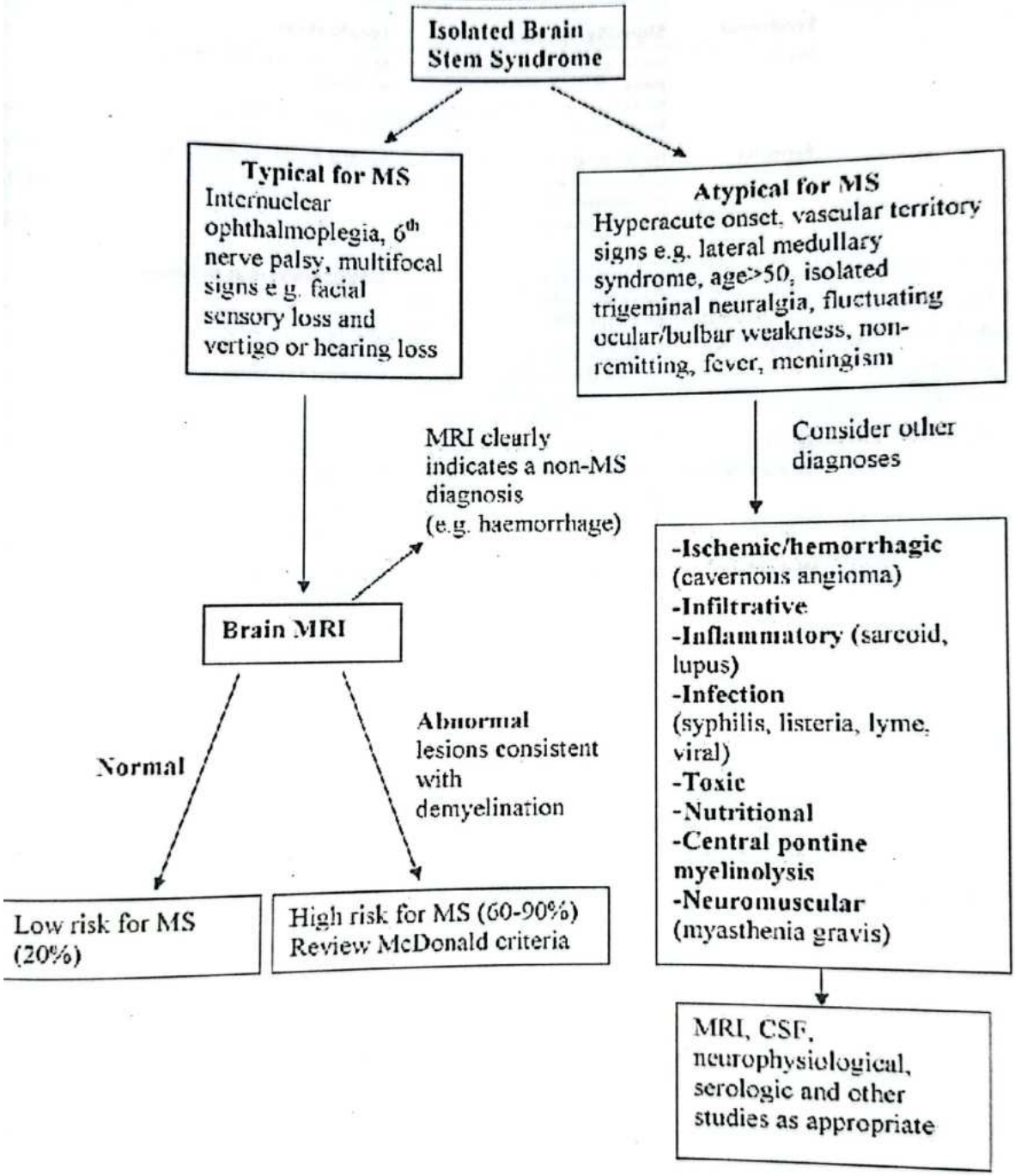
Differential diagnosis of brain stem syndrome :

1. Ischemia- stroke (PICA, AICA, WEBERS)
2. Demyelinating disease (NMOSD)
3. Brain stem encephalitis
4. Cerebral pontine myelinosis
5. Basilar type migraine
6. Skull base osteomyelitis
7. Miller Fischer syndrome
8. Wernickes encephalopathy

Signs and symptoms :

1. Opthalmoplegia especially if involving more than one year movement.
2. Conjugate gaze palsy
3. Pupil involvement either as 3rd nerve palsy or as central horner
4. Nystagmus especially if vertical.
5. Crossed hemiplegia or sensory dysfunction
6. Ataxia in combination with any of the above
7. Bilateral pyramidal signs e.g, extensor plantars or quadriparesis
8. Autonomic involvement

Scanned with CamScanner


Isolated Brain Stem Syndrome
Typical for MS
Internuclear ophthalmoplegia, 6th nerve palsy, multifocal signs e g. facial sensory loss and vertigo or hearing loss
Atypical for MS
Hyperacute onset, vascular territory signs e.g. lateral medullary syndrome, age>50, isolated trigeminal neuralgia, fluctuating ocular/bulbar weakness, non-remitting, fever, meningism
MRI clearly indicates a non-MS diagnosis (e.g. haemorrhage)
Consider other diagnoses
Brain MRI
Normal
Abnormal lesions consistent with demyelination
Low risk for MS (20%)
High risk for MS (60-90%) Review McDonald criteria
-Ischemic/hemorrhagic (cavernous angioma)
-Infiltrative
-Inflammatory (sarcoid, lupus)
-Infection (syphilis, listeria, lyme, viral)
-Toxic
-Nutritional
-Central pontine myelinolysis
-Neuromuscular (myasthenia gravis)
MRI, CSF, neurophysiological, serologic and other studies as appropriate

Scanned with CamScanner

Syndrome	Signs/Symptoms	Localization
Weber	Ipsilesional cranial nerve III palsy, contralesional hemiparesis (including the lower face)	Medial midbrain/cerebral peduncle
Benedikt	Ipsilesional cranial nerve III palsy, contralateral involuntary movements (intention tremor, hemichorea, or hemiathetosis)	Ventral midbrain involving red nucleus
Nothnagel	Ipsilesional cranial nerve III palsy, contralesional dysmetria, and contralesional limb ataxia	Superior cerebellar peduncle
Foville	Ipsilateral cranial nerves VI and VII (lateral gaze palsy, upper and lower facial weakness), with or without contralateral hemiparesis	Caudal pontine tegmentum involving the facial colliculus
One-and-a-half	Ipsilateral cranial nerve VI (lateral gaze) palsy, bilateral internuclear ophthalmoplegia	Paramedian pons involving the paramedian pontine reticular formation and medial longitudinal fasciculi
Wallenberg	Ipsilesional facial and contralesional body hypalgesia and thermoanesthesia; ipsilesional palatal weakness; dysphagia, dysarthria, nystagmus, vertigo, nausea/vomiting; ipsilesional oculosympathetic defect (Horner syndrome); skew deviation, singultus	Lateral medulla
Dejerine	Ipsilesional tongue weakness and contralesional hemiparesis with or without contralesional loss of proprioception and vibratory sense	Medial medulla

Investigations :

1. MRI brain
2. MRA head
3. CSF RE, OCBs
4. VDRL, TPHA, CHEST X-RAY
5. Vit B12 folate levels, red cell transketolase levels.
6. NCS/EMG

Treatment

1. For vascular territory syndrome management same as of strike
2. For demyelinating etiologies high dose corticosteroid and plasma exchange
3. For Wernickes replacement of thiamine.

Scanned with CamScanner

MOTOR NEURON DISEASE

Lesions: UMN+LMN Lesion + bulbar symptoms
UMN only
LMN only.

Case:

As per Command, I have done the motor examination of the patient. The upper limbs show proximal and distal wasting with prominent fasciculation. There is wasting of small muscles of the hands. There is hypertonia and hyper reflexia. The lower limb show proximal and distal wasting with prominent fasciculation. There is hypertonia and hyper reflexia. There is extensor plantar response and sensation is normal. Patient has dysarthria with nasal quality speech. The patient demonstrates a combination of upper and lower motor neuron signs with no sensory signs. My top most differential is motor neuron disease.

Differential diagnosis ;

1. **Disorders affecting UMN +LMN dysfunction**
   Structural Lesions affecting brain stem and spinal cord
   - Parasaggital tumors
   - Foramen magnum tumour
   - Cervical Spondylosis
   - Synringomyelia
   - Sub -acute combined degeneration
2. **UMN disorder**
   - Hereditary Spastic paraparesis
   - Primary lateral sclerosis
3. **LMN disorder with motor neuropathy**
   - Multi focal motor neuropathy with conduction block
   - Spinal muscular atrophy
   - Monomelic Motor neuron disease
   - Polyradiculopathy and poly neuropathy
4. **Myopathy**
   - Inclusion body myositis

Classification Of Motor Neuron Disease :

Acute:
Lower motor neuron only e.g poliomyelitis

Chronic:
UMN AND LMN e.g, ALS

Scanned with CamScanner

UMN e.g. Primary lateral sclerosis
LMN e.g. Progressive spinal muscular atrophy
Monomelic muscular atrophy

Diagnostic Criteria Of ALS:

Definite ALS: UMN and LMN signs in at least 3 body regions

Probable ALS: UMN and LMN signs in at least 2 body regions with some UMN signs rostral LMN signs.

Clinically probable lab supported ALS

UMN signs with or without LMN signs in at least 2 regions, neuro imaging, and lab study t exclude other criteria.

Possible ALS

UMN and LMN signs in 1 region
UMN signs in at least 2 regions
UMN signs caudal to LMN

Suspected ALS:

Pure LMN signs.

Types of Motor neuron disease:

- Amyotrophic lateral Sclerosis
- Primary lateral sclerosis
- Progressive Muscular Atrophy
- Progressive bulbar palsy

Signs and Symptoms :

Initial presentation

May occur in anybody segments (bulbar, cervical, thoracic or lumbosacral) may Manifest as upper motor neuron or lower motor neuron signs.

- Asymmetric limb weakness is most common presentation. The split hand syndrome describes a frequent pattern of weakness and atrophy in ALS that predominantly involves the median and ulnar innervated hand muscles with sparing of hypothenar muscle
- Lower limb signs include foot drop
- Bulbar symptoms like dysarthria, Dysphagia
- Pseudo bulbar affect manifested as inappropriate laugh, crying or yawning
- May have laryngospasm , difficulty closing or opening mouth.
- May have cognitive impairment typically related to fronto temporal dementia may be associated with ALS
- Extrapyramidal symptoms and signs of Parkinsonism may precede or follow upper and lower motor neuron symptoms
- Sensory impairment may occur in 20 to 30 percent of patients

Investigations :

1. **NCS/EMG**

Scanned with CamScanner

Confirmation of lower motor neuron dysfunction in patients with ALS and LMN disorder

2. **MRI brain and Spine**
   Detection of corticospinal tract abnormalities in ALS
3. **Lumbar puncture:**
   Detection of inflammatory process , elevated proteins may indicated polyneuropathy, Polyradiculopathy and Lymphoma.
4. **Serologic studies:**
   Serum and urine electrophoresis, immunofixation electrophoresis, immunoglobulin, monoclonal gammopathy.

Treatment :Disease Modifying therapies :

1. **Initial treatment with Riluzole:**

Riluzole has been shown to prolong survival and slow progression. Administration is by tablet at 50mg BD

2. **Injection Edavarone**

Given as IV infusion once daily, initial dosing is 14 days on treatment followed by 14 days off treatment the maintenance dosing at 10 days within 14 days interval treatment followed by 14 days off

Symptomatic Management :

Depression: Amitriptyline may be used.

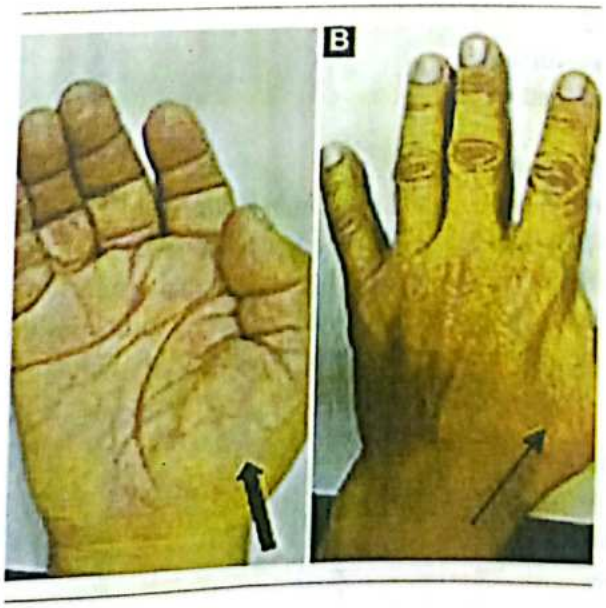
Drooling: Anti cholinergic drugs, Tricyclic antidepressants

Communication: Speech and language therapist

Dysphagia: PEG tube insertion

Respiratory problem: Suction and non-invasive respiratory support

fasciculation : Magnesium , Vit E , Diazepam



Scanned with CamScanner

Spasticity : Baclofen, Dantrolene.

Slit hand sign in MND ALS

Lower Motor Neuron Lesions

Can be divided into:

1. **Lower motor neuron Lesions with wasting:**
    - Lower motor neuron Lesions with wasting and normal sensation
        - ❖ Myopathies
        - ❖ Ant horn cell disorder
        - ❖ Pure motor polyneuropathy
    - Lower motor neuron lesion with wasting and abnormal sensory examination
        - ❖ All peripheral nerve Lesions and radiculopathy, mono neuropathies and plexopathies.
2. **Lower motor neuron lesion without wasting**
    - Lower motor neuron lesion without wasting and normal sensory examination
        - ❖ Myopathy
        - ❖ NMJ disorder
        - ❖ Pure motor polyneuropathy
    - Lower motor neuron Lesions without wasting and abnormal sensory examination
        - ○ Includes all peripheral nerve Lesions of LMN like radiculopathy

Peripheral Neuropathy

Lesions:

- Sensory Neuropathy
- Motor Neuropathy
- Sensorimotor Neuropathy
- Autonomic Neuropathy

CASE:

As per Command, I have examined the lower limbs of the patient . On examination, the skin was shiny , dry with loss of hair upto calves. There are ulcers present on the sole of the feet. There is no weakness, wasting. Reflexes are preserved. There is bilateral symmetric sensory loss in a stocking distribution accompanied by impaired light touch , pinprick , joint position and vibration. There is also ataxia and wide gait. Rhombergs sign is also present. My top most differential is peripheral sensory neuropathy.

Symptoms of neuropathy :

Motor neuropathy:

- Weakness
- Fatigue

Scanned with CamScanner

- Hypotonia
- Loss of reflexes
- fasciculation
- Cramps
- Deformity

Sensory neuropathy :

Large fibers

- Tingling
- Pins and needles
- Decreased vibration
- Decreased joint position sense
- Are flexible
- Hypotonia

Small fibers

- Burning, jabbing , shooting pain
- Decreased pin prick
- Decreased temperature

Autonomic dysfunction :

- Increased heart rate
- Urinary retention
- Inadequate bowel emptying
- Anhidrosis

Differential Diagnosis :

Sensorimotor polyneuropathy :

- Alcohol
- Diabetes
- Hypothyroidism
- Sarcoidosis
- Uremia
- CIDP
- GBS
- Vasculitis
- HMSN

Motor neuropathy:

- Porphyria
- Lead
- Diphtheria
- CIDP
- GBS

Scanned with CamScanner

Sensory neuropathy :

- Alcohol
- Diabetes
- Hypothyroidism
- B12 deficiency
- Infections like leprosy, Lyme
- Uremia

Autonomic :

- Guillain barre syndrome
- Botulism
- Porphyria
- Paraneoplastic

Large fibre neuropathy	Small fibers neuropathy
Numbness, pins and needles, Tingling sensation, gait imbalance	Burning pain, allodynia
Decreased position and vibration sense	Decreased pin prick and temperature sense
Decreased reflexes	Preserved reflexes

Demyelinating	Axonal
Vibration and proprioception affected more than pain and temperature	Pain and temperature affected more than. Vibration and proprioception
Proximal and distal weakness are same	Distal weakness is more than proximal weakness
Recovers fast If treated on time	Slow recovery
Examples: Multiple myeloma, MGUS, HMSN, Multifocal motor neuropathy, POEM syndrome	Examples: Diabetes

Scanned with CamScanner

Causes of thickening of Peripheral nerves:

- Amyloidosis
- Hereditary motor and sensory neuropathy
- Leprosy
- Acromegaly
- Neurofibromatosis

Investigations :

- Full blood count
- ESR, Urine RE
- Thyroid function test
- B12 and folate levels
- Autoimmune profile
- NCS EMG
- CSF RE
- Nerve biopsy

Treatment :

Depends on underlying cause

- Diabetic neuropathy requires adequate Diabetic control
- GBS need urgent plex or IVIG
- CIDP needs IV Methylprednisolone and plasmapheresis
- Duloxetine and Gablins for sensory neuropathy
- Tramadol and NSAIDS for any pain.

Scanned with CamScanner

GUILLIAN BARRE SYNDROME:

Demyelinating Polyradiculopathy
Acute< 4 weeks
Subacute 4 to 8 weeks
Chronic > 8 weeks

Case

As per Command, I have done the motor examination of the lower limbs of this patients . On examination, the patient has hypotonia, power is 2/5 in both lower limbs, and there is arefelexia, bilateral mute plantars. The extraocular muscles movement is intact, no cranial nerve palsies are present. Patient had tracheostomy scar visible in neck, single breath count is more than 10. My topmost differential diagnosis is Guillain barre syndrome.

Differential Diagnosis :

1. CIDP
2. Myasthenia Gravis
3. Hypokalemic Periodic paralysis
4. MND

Gillian Barre syndrome :

GBS is an acute , inflammatory, demyelinating Polyradiculopathy that has many clinical variants and pathogenic mechanism that lead to axonal , demyelinating or mixed findings in electro diagnostic variants.

Infections are most common antecen before GBS.

Some Infections leading to GBS include :

1. Campylobacter jejuni
2. Hep E virus
3. Cytomegalovirus
4. Eastern bar virus
5. Mycoplasma Pneumonia

Clinical Course :

- **Prodormal phase:**
  Is characterized by antecedent event, could be infectious or non- infectious, triggering a breakdown in immune tolerance and subsequent initiation of immune mediated process.
- **Progressive Phase:**
  Development of neuropathy symptoms, which by definition should not progress beyond 4 weeks. Symptoms typically read a clinical nadir at 2 weeks however, weakness can rapidly progress in 24 hours leading to intubation.

- **Plateau phase:**
  Lasts for 1 to 4 weeks and subsequently enter phase of recovery.

Diagnostic Criteria For GBS:

Features required for Diagnosis:

Scanned with CamScanner

1. Progressive weakness of more than one limb
2. Arefelexia or Hyporeflexia.

Features that strongly support GBS Diagnosis :

1. Progression of symptoms over days to 4 weeks
2. Relative symmetry of symptoms
3. Mild sensory symptoms or signs
4. Cranial nerve involvement especially bilateral
5. Autonomic dysfunction
6. Elevated CSF proteins.

GBS Classification :

1. **Clinical :**

- **Weakness not prominent :**
  - Acute dysautonomia
  - Miller Fischer syndrome
  - Bicker staff encephalitis
  - Pure sensory variant.
- **Weakness prominent :**
  - Generalized
  - Localized
    - Pharyngeocervical brachial
    - Paraparesis with bladder involvement
    - Acute bulbar palsy.

2. **Neurophysiological:**

- Demyelinating
  - AIDP
- Axonal
  - AMAN
  - AMSAN

Miller Fischer Variant of GBS:

A spectrum of disorder with anti gangliosode GQ1B antibodies in 85 to 90 percent of the
Complete form is characterized by

1. Opthalmoplegia
2. Ataxia
3. Arefelexia

Treatment is similar to GBS other variants. If symptoms do not improve wait and watch n
recover spontaneously after 6 months.

Scanned with CamScanner

Investigations :

1. CSF studies
   Mild pleocytosis of 10 to 20 cells /mm^3 is seen in upto 5 percent of the patients.
2. Electro diagnostic studies:
   For accurate diagnosis of GBS subtypes patient may require two studies 1 and 3 weeks apart.
   Findings include early-prolonged latencies or absent F waves.
3. Neuroimaging :
   Spinal MRI can demonstrate thickening and enhancement of intrathecal spinal nerve roots supportable diagnosis of GBS with a sensitivity of 83 percent .

Treatment :

If Patient Has Bulbar Symptoms :

If the patient has dysautonomia, bulbar dysfunction, rapidly worsening weakness, inability to count to 15 in single breath or signs of impending respiratory failure i.e. if vital capacity <20 ml /kg then the patient needs ICU care and mechanical ventilation.

4. Admit patient in ICU
5. Respiratory distress then mechanical ventilation
6. Pass double lumen
7. 5 sessions of plasmapheresis, 3 sessions consecutive and last two on alternate days with FFPs or Ringer lactate may be used
8. If plasmapheresis not available may use IVIG at 0.4g/kg daily for 5 days

If Patient Has No Bulbar Symptoms :

1. Admit patient in ward
2. Pass double lumen and do 5 sessions of plasmapheresis with FFPs or Ringer lactate.
3. Monitor for signs of distress if present shift patient To ICU.

Scanned with CamScanner

CHRONIC INFLAMMATORY DEMYELINATING POLYNEUROPATHY

Difference between CIDP VS GBS:

CIDP presents with symmetric proximal and distal weakness in upper and lower extremity with sensory loss affecting at least two limbs with areflexia that is progressive over time period greater than 2 months.

GBS tends to reach a nadir within 4 to 8 weeks and is mostly having a preceding infection , autonomic dysfunction, respiratory compromise , bifacial weakness.

Types of CIDP:

1. **DISTAL CIDP:**
   Symmetric sensory loss and distal weakness in the upper limbs and lower limbs with gait abnormality
2. **MULTIFOCAL CIDP :**
   Variant of CIDP that can present clinically with asymmetric weakness and sensory loss affecting both upper and lower limb.
3. **FOCAL CIDP:**
   Present with symptoms localizable to the brachial and lumbosacral plexus or single nerve of one limb and clinically manifesting with motor weakness , sensory symptoms.
4. **SENSORY CIDP/ CISP:**
   Pure sensory symptoms in a proximal and distal pattern with Absent or reduced reflexes. NCS/EMG shows normal sensory response and normal conduction of nerves.

Differential Diagnosis :

1. Charcot Marie tooth disease
2. MMN
3. MND
4. Idiopathic axonal neuropathy
5. Anti MAG
6. Anti paranodal and anti- nodal CIDP
7. CANOMAD
8. POEMS

Investigations :

1. Imaging
   MRI of the Cervical or lumbar spine is performed with without contrast to determine if enlargement, hyper intensity , or enhancement of nerve root is present.
2. CSF RE
   A CSF pleocytosis greater than 10 cells and particularly greater than 50 cells should raise suspicion of infection or inflammation. Proteins greater than 100mg/dl should strongly raise suspicion of of CIDP.

Scanned with CamScanner

TREATMENT :

IVIG

Intravenous or subcutaneous Immunoglobulin's
Induction dosage 2g/kg divided over 4 to 5 days
Maintenance 1g/kg every 3 to 4 weeks.

Corticosteroids

Start 20 to 60mg oral prednisone or IVMP 1000mg for 5 days

Plasma Exchange

First line treatment
Start plasmapheresis with FFPs for 5 days .
If unresponsive to Plasmapheresis or IV MP then Cyclophosphamide or rituximab may be used

MYASTHENIA GRAVIS

Case:

As per Command, I have examined this patient. The patient has bilateral ptosis, lack of facial expression, and midline scar on chest. the patients voice is weak with nasal twang. On motor examination patient has proximal muscle weakness with normal reflexes and sensations and he has a waddling gait. He has a single breath count upto 20, cough and gag are intact along with extraocular movements. My top most differential will be Myasthenia Gravis.

Differential Diagnosis :

1. Lambert Eaton
2. Botulism
3. Chronic progressive Opthalmoplegia
4. Miller Fischer syndrome
5. Snakebite

Types of Myasthenia Gravis:

1. Ocular Myasthenia Gravis
2. Generalized Myasthenia Gravis

Severity Grades of Myasthenia Gravis:

Class I :

Any eye muscle weakness , possible ptosis, no other evidence of muscle weakness elsewhere.

Class II:

Eye muscle weakness of any severity , mild weakness of other muscles.

Class IIa : Predominantly limb or axial muscles.

Class IIb : Predominantly bulbar or respiratory muscles.

Scanned with CamScanner

Class III :

Eye muscle of any severity , moderate weakness of other muscles

Class IIIa : Predominantly limb or axial muscles

Class IIIb : Predominantly bulbar or respiratory muscles.

Class IV:

Eye muscle weakness of any severity ,severe weakness of other muscles

Class IV a: Predominantly limb or axial muscle

Class IV b: Predominantly bulbar or respiratory muscles.

Class V:

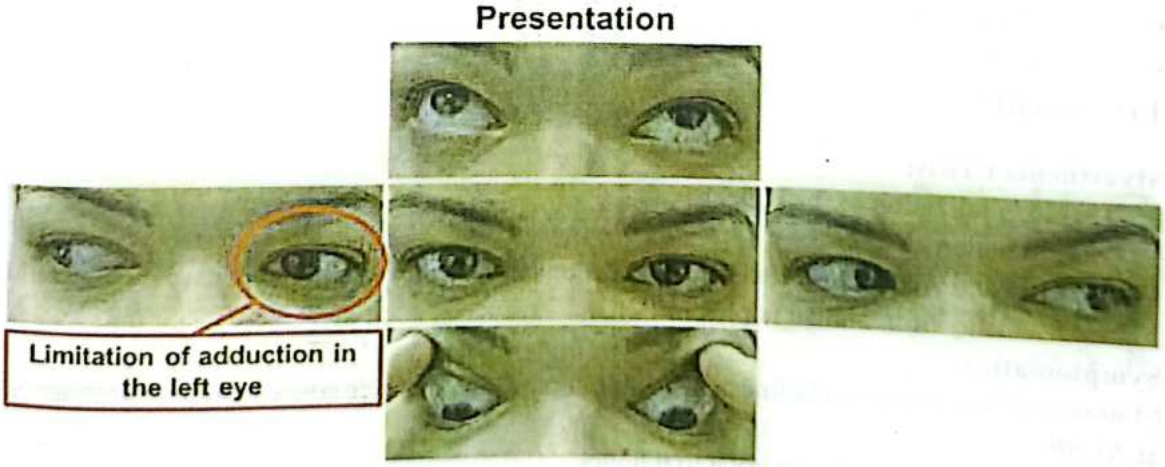
Intubation needed to maintain airway.

Important Signs Of Myasthenia Gravis:

1. Cogan lid twitch sign

- **Cogan's lid twitch sign:- when the patients are made to look down for 10 to 20 seconds and then asked to look up the upper lid will overshoot upward and twitch a few times before settling down. This upshoot is due to build up of ACh when the lid is resting and, easy weakening of the muscle after rapid elevation.**
- **This may occur in brain stem lesions and other oculo motor nerve lesions also**
- **Sometimes transient eye lid retraction also can occur**

2.



3. **Pseudo INO:**
4. Fluttering of the ptotic eyelid may be seen during Eye movements (lid hopping sign)
5. Peek signs- weakness of eye closure
6. Myasthenia snarl
7. Jaw supporting sign.
8. Herings law:

Scanned with CamScanner

In patients with myasthenia Gravis when a ptotic eyelid is lifted manually, there is no longer a requirement for excessive eyelid innervation, and as a result of reduction in eyelid innervation the other eyelid becomes ptotic.

	Myasthenia Gravis	Lambert Eaton
Antigenic Target	Post synaptic nACR	Presynaptic voltage-gated calcium channels
Diplopia	Common	Rare
Ptosis	Common	Rare
Tendon Reflexes	Normal	Reduced
Weakness	Proximal weakness upper limb> lower limb	Proximal weakness lower limb > upper limb
Autonomic dysfunction	No	Yes
Association	Autoimmune	Small cell Ca
RNS	Decremental	Incremental
Treatment	Acetylcholinesterase inhibitors Immunotherapy	Treatment of underlying tumour 3,4 diaminopyridine

Investigations :

- Ice pack test
- Tensilon test
- Anti Ach R antibodies
- Anti-MUSK antibodies
- NCS/EMG with RNS
- CT chest for thymoma

Treatment :

Myasthenia Crisis:

1. Hospitalization of the patient
2. Intubation
3. Stop anti Acetylcholinesterase medication because they can promote excessive secretions
4. Mainstay of treatment is plex or IVIG

Symptomatic :

Mainstay of Treatment is cholinesterase inhibitors, which increase concentration of acetylcholine at AChR

Pyridostigmine 600mg /day every 4 to 6 hours

Immunosuppressive :

1. Thymectomy

   Antibody positive myasthenia Gravis and thymectomy is best treatment with fewer exacerbations.

Scanned with CamScanner

Before thymectomy is planned , start medical therapy and complete 5 sessions of plasmapheresis.

2. Corticosteroid :
   First line Immunosuppressive Treatment
   May have Transient worsening of symptoms
   Remissions in upto 50 percent of patients and upto 80 percent patients have benefit.
3. Non-steroidal Immunosuppression:
   - Steroid sparing agents like azathioprine at least 50 percent of patients benefit.
   - Mycophenolate mofetil, cyclosporine, Cyclophosphamide may also be used.
   - Rituximab, a monoclonal antibody targeting CD 20 a B lymphocyte antigen may be used.

Medicine that exacerbate MG:

1. Aminoglycosides
2. Beta Blockers
3. Calcium Channel Blockers
4. Chloroquine
5. D-penicillamine
6. Phenothiazine's
7. Lithium
8. Quinine

Scanned with CamScanner

MUSCULAR DYSTROPHY

Case:

As per Command, I have examined the motor systems of this man. On examination, he has myopathic face, as evident by wasting and weakness of facial muscles. On upper limb examination, there is weakness and wasting of upper limb girdle muscles ,there is winging of scapula. There is also weakness of foot dorsiflexion and patient has foot drop. My topmost differential is fascio-scapulohumeral dystrophy.

Differential diagnosis :

1. Fascio-scapulohumeral dystrophy
2. Myotonic dystrophy
3. Oculopharyngeal muscular dystrophy
4. Nemaline myopathy

Classification of muscle disease:

INHERITED :

1. Muscular dystrophy
   Dystrophinopathies limb girdle muscular dystrophy, myotonic dystrophy, fascio-scapulohumeral , congenital muscular dystrophy
2. Mitochondrial myopathy
3. Metabolic Myopathies
4. Congenital myopathies
5. Channelopathies.

Acquired :

1. Inflammatory / immune myopathy
2. Drug and toxin induced
3. Endocrine related.

Duchene Muscular dystrophy :

- Affects males
- X linked recessive inheritance
- Starts before 5 years of age
- Proximal ms weakness
- Has Gower signs and calf muscle pseudohypertrophy
- Elevated CK levels almost 10 fold
- Life threatening vulnerability to malignant hyperthermia from anesthesia

Becker's muscular dystrophy:

- Typically affects males
- After 12 years of age
- Proximal ms weakness and calf pseudohypertrophy

Scanned with CamScanner

- Elevated CK levels 5 fold.

Myotonic dystrophy :

- Most prevalent form of muscular dystrophy in adults
- DM1 and DM2 transmitted as autosomal dominant
- Slowly progressive weakness of facial and SCM muscles , occurs in association with frontal balding, ptosis and temporal wasting.
- Bulbar and neck muscles may be involved
- Distal muscles are more severely affected than proximal ms
- Myotonia is Characteristic findings
- Most patients have cardiac involvement (heart block and cardiomyopathy)

Fascio-scapulohumeral dystrophy:

- LGMD-1 autosomal dominant
- LGMD-2 autosomal recessive
- Slowly progressive pelvic and shoulder girdle weakness is often seen
- May have cardiomyopathy and calf pseudohypertrophy

Emery dreiefus muscular dystrophy :

- X linked recessive
- Proximal early contracture
- Weakness and atrophy of humeral and peroneal muscles
- Classic triad: Prominent early contracture Weakness and atrophy of humeral and peroneal muscles
- Cardiac conduction defects
- CK level may be elevated

Investigations :

1. Muscle biopsy
2. MRI e T1 W , T2W, STIR sequences
3. Serum CK levels
4. EMG

Treatment:

Muscular dystrophy:

1. Steroid like prednisone 0.75 mg/kg
2. Monitoring of Cardiac functions
3. Use of ACE Inhibitors
4. MDT approach involving orthopedics, physiotherapist, cardiologist.

Exondyl 51 new treatment for DMD

Symptomatic Treatment for all others

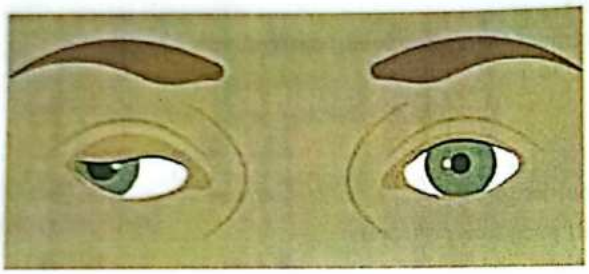
Scanned with CamScanner

Oculomotor Nerve 3rd Cranial Nerve

Three important signs

1. Ptosis
2. Mydriasis (pupil sparing or pupil involved)
3. Down and out

RIGHT 3rd NERVE PALSY



Symptoms

- Binocular diplopia (horizontal, vertical or oblique diplopia with droopy eyelid)
- Pain accompanying the onset of third nerve palsy is common except in mid brain lesion.

On Examination :

1. **Complete non- pupil sparing 3rd Cranial nerve palsy**

- Ptosis
- Large un reactive pupil
- Paralysis of adduction, elevation and depression
- Eye rests in a position Of abduction, slight depression and extrusion (down and out)

2. **Partial lesion**

- Ptosis
- Pupil may be of normal size and normally reactive (no internal dysfunction)
- Dilated and poorly reactive (partial internal dysfunction)
- Dilated and non- reactive to light and near stimulus (complete internal dysfunction)
- There may be complete or incomplete involvement of extraocular muscles (external dysfunction)
- May have different degrees of ptosis and weakness of ipsilateral addiction (medial rectus) elevation (superior rectus, inferior oblique) or depression (inferior rectus)

Scanned with CamScanner

Causes:

ICA (PCOM/ basilar) , PCA aneurysm
Microvascular (ischemic)
Tumor (pituitary, carcinomatosis, Meningitis)
Herniation
Trauma

Cavernous Sinus:

Signs/symptoms :

CN IV ,VI,V1 and V2
Horner syndrome
Pain may be prominent

Causes:

Tumour
Inflammation
Carotid aneurysm
Thrombosis
AV fistula

Orbital apex:

Signs/ symptoms :

Proptosis, visual loss, CN IV, VI, V1, V2
Horner syndrome, pain

Causes

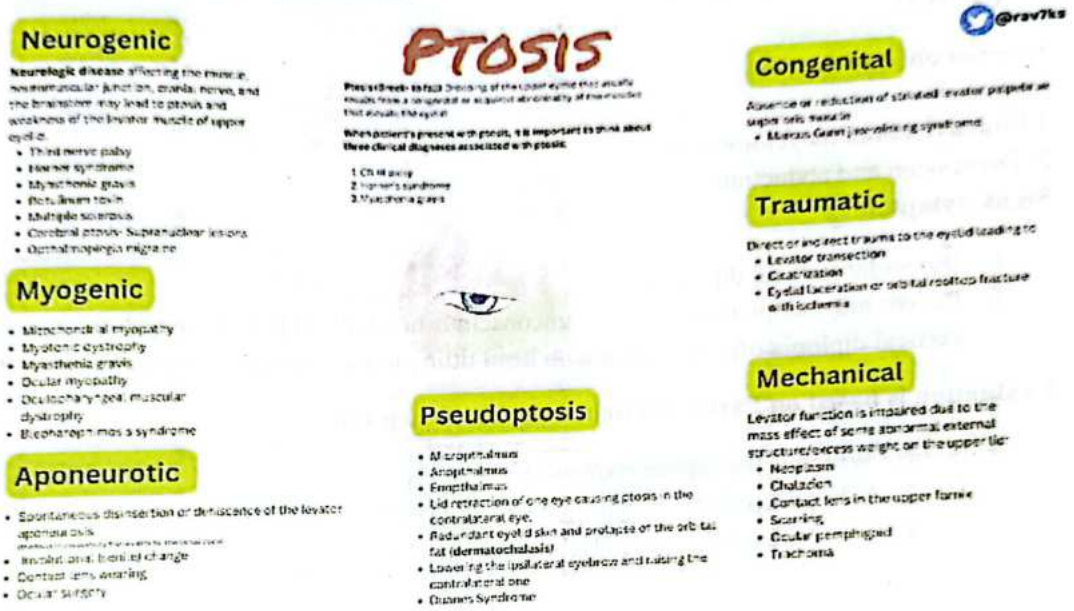
Trauma , tumour, Inflammation, fungus.

CAUSES OF BILATERAL PTOSIS:

- Myasthenia Gravis
- Myotonic dystrophy
- Chronic progressive external Opthalmoplegia

Scanned with CamScanner

- Kearns-Sayre syndrome


PTOSIS
@ravi7ks
Neurogenic
Neurologic disease affecting the muscle, neuromuscular junction, cranial nerves, and the brainstem may lead to ptosis and weakness of the levator muscle of upper eyelid.
• Third nerve palsy
• Horner syndrome
• Myasthenic gravis
• Botulinum toxin
• Multiple sclerosis
• Cerebral ptosis- Supranuclear lesions
• Opthalmoplegia migraine
Myogenic
• Mitochondrial myopathy
• Myotonic dystrophy
• Myasthenia gravis
• Ocular myopathy
• Oculopharyngeal muscular dystrophy
• Blepharophimosis syndrome
Aponeurotic
• Spontaneous dehiscence of the levator aponeurosis
• Involutional tissue change
• Contact lens wearing
• Ocular surgery
When patient's present with ptosis, it is important to think about three clinical diagnoses associated with ptosis.
1. CN III palsy
2. Horner's syndrome
3. Myasthenia gravis
Pseudoptosis
• Microphthalmus
• Anophthalmus
• Enopthalmos
• Lid retraction of one eye causing ptosis in the contralateral eye.
• Redundant eyelid skin and prolapse of the orb tal fat (dermatochalasis)
• Lowering the ipsilateral eyebrow and raising the contralateral one
• Duanes Syndrome
Congenital
Absence or reduction of striated levator palpebr ae superioris muscle
• Marcus Gunn jaw-winking syndrome
Traumatic
Direct or indirect trauma to the eyelid leading to
• Levator transection
• Cicatrization
• Eyelid laceration or orbital roof/floor fracture with ischemia
Mechanical
Levator function is impaired due to the mass effect of some abnormal external structure/excess weight on the upper lid
• Neoplasm
• Chalazion
• Contact lens in the upper fornix
• Scarring
• Ocular pemphigoid
• Trachoma

Evaluation :

1. Non isolated 3rd CN palsy
   - MRI brain
   - LP for CSF RE to rule out infection.
2. Isolated 3rd CN palsy
   - CTA head to rule out aneurysm or MRA
   - CT brain or MRI brain to rule out SAH or ischemic infarct.

Treatment :

1. Aneurysmal 3rd CN palsy
   Intervention- Treatment of choice coiling or clipping.
2. Ischemic 3rd CN palsy
   Diabetic mostly
   Usually improves over 3 to 6 months
   Antiplatelet and optimum Diabetic control
3. Opthalmoplegia migraine
   Treatment of migraine
4. Inflammatory / infection
   Treatment of fungus/ Meningitis

Scanned with CamScanner

TROCHLEAR NERVE PALSY (4th Cranial Nerve)

Supplies:

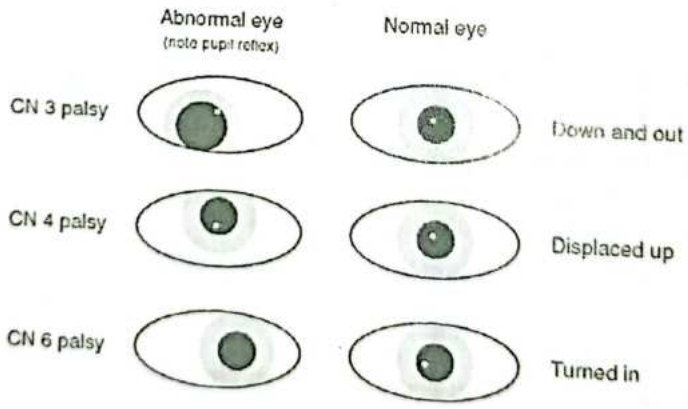
Superior oblique muscles
Function
1.Primary action: incyclotorsion
2. Depression and abduction.

Signs/ symptoms :

1. Binocular vertical diplopia
2. Patient may adopt a conscious or unconscious head tilt. This is because torsional and vertical diplopia often improve with head titling to the opposite side of the muscles.

Evaluation is based on Parks- Bielschowsky three-step test:

1. Which is the higher eye?
2. Is hypertropia worse on right or left gaze ?
3. Is hypertropia worse in right or left head tilt?



A right trochlear nerve palsy may present as:

4. Right hypertropia in primary position.
5. Right hypertropia worse in left gaze
6. Right hypertropia worse with right head tilt.

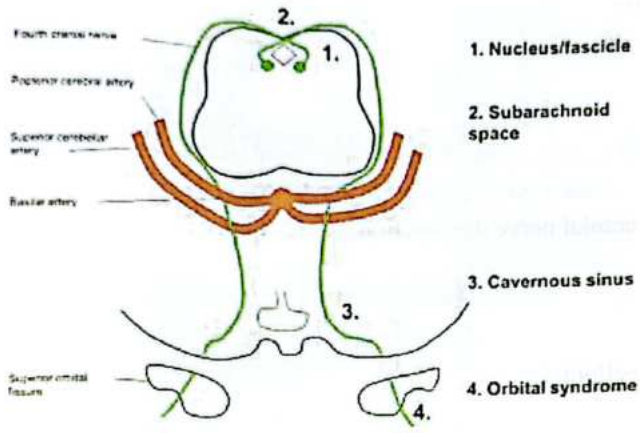
DIFFERENTIAL DIAGNOSIS :

1. Grave opthalmoplegia
2. Myasthenia Gravis
3. Intra Orbital Tumor
4. Trauma

Etiologies Of 4TH CN Palsy:

Scanned with CamScanner

Lesion Sites and Causes:



Anatomical course of the 4th cranial nerve with possible lesion sites

1. Midbrain: Nuclear / fascicular

Clinical features:

- Hemisensory loss
- Hemiparesis
- Central horner syndrome
- Brain stem cranial neuropathies.

Causes:

- Aplasia of nucleus
- Vascular lesion in brain stem (AVM)
- Demyelination
- Brain stem hemorrhage
- Infarction
- Trauma
- Tumor

2. Subarachnoid space

Clinical features

- Headache
- Stiff neck
- Cranial nerve abnormalities

Scanned with CamScanner

Causes :

- Aneurysms e.g superior cerebellar artery
- Increased ICP
- Infection like mastoiditis
- Post LP/ spinal anesthesia
- Trauma
- Neoplasm

3. Cavernous Sinus

Clinical features:

- Third , fifth , sixth cranial nerve dysfunction
- Horner syndrome

Causes

- Neoplasm
- Infections like Orbital cellulitis
- Infiltration (sarcoid)
- Trauma
- Inflammation

Investigation

Individuals who have non- isolated fourth nerve palsies with neurologic signs and symptoms that localize to brain stem subarachnoid space or Cavernous Sinus or Orbit should undergo imaging. Whereas those with isolated fourth nerve palsy that seems traumatic , congenital or ischemic do not require imaging.

MRI Brain with contrast is sensitive in detection of non- isolated fourth nerve palsy.

Additionally lumbar puncture in patients that have normal imaging studies but have suspicion of Meningitis process.

Treatment :

Treat the underlying etiology e.g brain tumor , ICP.

Microvascular lesion are likely to improve and resolve over months. Traumatic palsies may resolve over months and If not should be considered for prism therapy.

Patching one eye will alleviate Binocular diplopia and is useful for patients who are being observed.

Scanned with CamScanner

ABDUCENT NERVE PALSY (6TH CRANIAL NERVE PALSY)

Supplies:

Lateral rectus

Function:

Abduction

Clinical manifestations :

- Horizontal diplopia
- Diplopia is Binocular and worsens with Horizontal gaze towards paretic lateral rectus
- Eye pain usually in microvascular cranial neuropathies.

ETIOLOGY OF ABDUCENT NERVE PALSY

Lesions with signs and symptoms

1. **Nuclear/ Fasicular Lesions in pons**

Signs/symptoms :

- Horizontal gaze palsy
- Ipsilateral facial palsy
- Other brain stem signs including hemiparesis, Hemisensory loss, Dysmetria encephalopathy, gait ataxia

Causes :

- Demyelinating Lesions
- Ischemic Lesions
- Neoplastic Lesions
- Wernickes encephalopathy

2. **Subarachnoid space lesion**

Causes	Signs
Increased ICP from any cause	May be bilateral having other signs of increased ICP
Microvascular 6th nerve palsy	Isolated CN palsy often with periorbital pain
Aneurysm (causing nerve compression)	Usually isolated CN palsy if unruptured aneurysm
Meningeal inflammation or infiltration from infection, neoplasia, inflammatory process.	Meningismus
Low ICP	Headache , nausea, vomiting

Scanned with CamScanner

Petrous apex lesion:

Signs:

- Facial pain (especially retro Orbital)
- 5^{th} , 7^{th} and 8^{th} cranial nerve involvement

Causes:

- Neoplasm
- Infection or inflammation
- Thrombosis of inferior Petrosal sinus
- Traumatic/ basilar , Skull, petrous apex fracture

Cavernous sinus lesions:

Signs:

- Impaired function of 3^{rd} ,4^{th} and 5^{th} cranial nerve
- Horner syndrome

Causes:

- Cavernous Sinus thrombosis
- Cavernous Sinus fistula
- Neoplasm/tumor
- Pituitary adenoma
- Infection or inflammation
- ICA aneurysm or dissection

Orbital lesions:

Signs/symptoms

- Variably affected CN 6, 7 and 8^{th}
- Proptosis and chemosis
- Compressive optic neuropathy

Causes:

- Neoplasia
- Infection
- Inflammation

Differential diagnosis :

- Thyroid eye disease
- Orbital myositis
- Myasthenia Gravis

Investigations :

- MRI brain and orbits with contrast
- LP for opening pressure
- CSF RE
- ESR, CRP, to rule out giant cell arteritis which can cause unilateral or bilateral 6^{th} nerve palsy

Scanned with CamScanner

Treatment :

1. Infection, inflammatory or neoplastic lesions should relieve appropriate therapy for underlying condition
2. In patients with GCA initiate glucocorticoid
3. Spontaneous recovery may occur in unilateral, isolated, non- traumatic 6th cranial nerve palsy
4. Traumatic is observed for months for Spontaneous recovery if not resolved then treated

Treatment modalities:

1. Patching of one eye alleviated Binocular diplopia in individual 6th nerve palsy
2. Prism therapy
3. Strabismus therapy
4. Botulinum toxin.

Important points:

Gradenigo syndrome : Localized inflammation of meninges at the petrous apex characterized by a 6th nerve palsy , 7th nerve palsy, ipsilateral facial pain , photo phobia, decreased corneal sensation (5th cranial nerve)

Seen in patients with severe mastoiditis. May also been seen with tumors aneurysm and lateral Sinus thrombosis.

Evaluation Of Diplopia :

1. which eye sees double false image?
2. where is image widest apart?

Lateral:

Parallel images. ⟹ 6th nerve palsy

Downward and medially:

Images at an angle. ⟹ 4th Cranial nerve palsy

All other directions. ⟹ Eye down and out with ptosis , 3rd nerve palsy

Scanned with CamScanner

7TH CRANIAL NERVE PALSY (FACIAL NERVE)

Signs/symptoms :

- Characterized by weakness of upper and lower portion of face
- Classic findings include eyebrow sagging , inability to close eye, disappearance of nasolabial fold and drooping of the affected corner of mouth.
- May be associated with sensory or autonomic dysfunction
- Ipsilateral impaired taste sensation or Ipsilateral decreased tearing
- Ipsilateral retro auricular pain and hyper causes.
- Onset of facial weakness in bell's palsy occurs over several hours , upto 72 hours symptoms may worsen for days upto 3 weeks the stabilize to improve.

Differential diagnosis:

1. Lyme disease
2. Herpes zoster
3. Tumor
4. GBS
5. Meningeal disease
6. Neurosarcoidosis
7. Sjogrens disease

Causes of facial nerve palsy:

Upper motor neuron lesion:

- Cerebrovascular accident
- Trauma
- Tumour
- Infection
- Multiple sclerosis

Lower motor neuron lesion:

1. **Systemic infection :**
   - Bell's palsy
   - Varicella zoster virus
   - Lyme disease
   - HIV infection
2. **Middle ear disease**
   - Otitis media
   - Cholesterol
3. **Lesion of base of Skull**
   - Fracture
   - Skull base osteomyelitis
4. **Parotid lesion**
   - Tumour

Scanned with CamScanner

- Trauma to branch of facial nerve.

V ascular	CVA / Cerebral Aneurism
I diopathic / iatrogenic	Post surgical to parotid, middle ear or internal acoustic meatus
T raumatic	Fractured temporal bone / laceration
A utoimmune	Sarcoid / Multiple Sclerosis / Guillain-Barré syndrome Melkerson-Rosenthal Syndrome
M etabolic	Diabetes mellitus
I nflammatory / infective	Acute suppurative otitis media, cholesteatoma, malignant otitis externa
	Ramsay Hunt syndrome
	Bell's Palsy
N eoplastic	Facial or vestibular schwannomas and malignancy in the parotid Mucoepidermoid or adenoidcystic carcinomas are rare but cause paralysis. Benign parotid tumours e.g. pleomorphic adenoma do not cause paralysis
D evelopmental	Moebius syndrome / Hemifacial microsomia

Bilateral Facial Nerve Palsy:

- Lyme disease
- Guillian barre syndrome
- Sarcoidosis
- Trauma to the temporal bones
- HIV
- Syphilis
-
- Amyloidosis

Scanned with CamScanner

- SLE
- Myasthenia Gravis
- Granulamatosis with polyangiitis
- Multiple sclerosis

House-Brackmann Facial Nerve Grading Scale

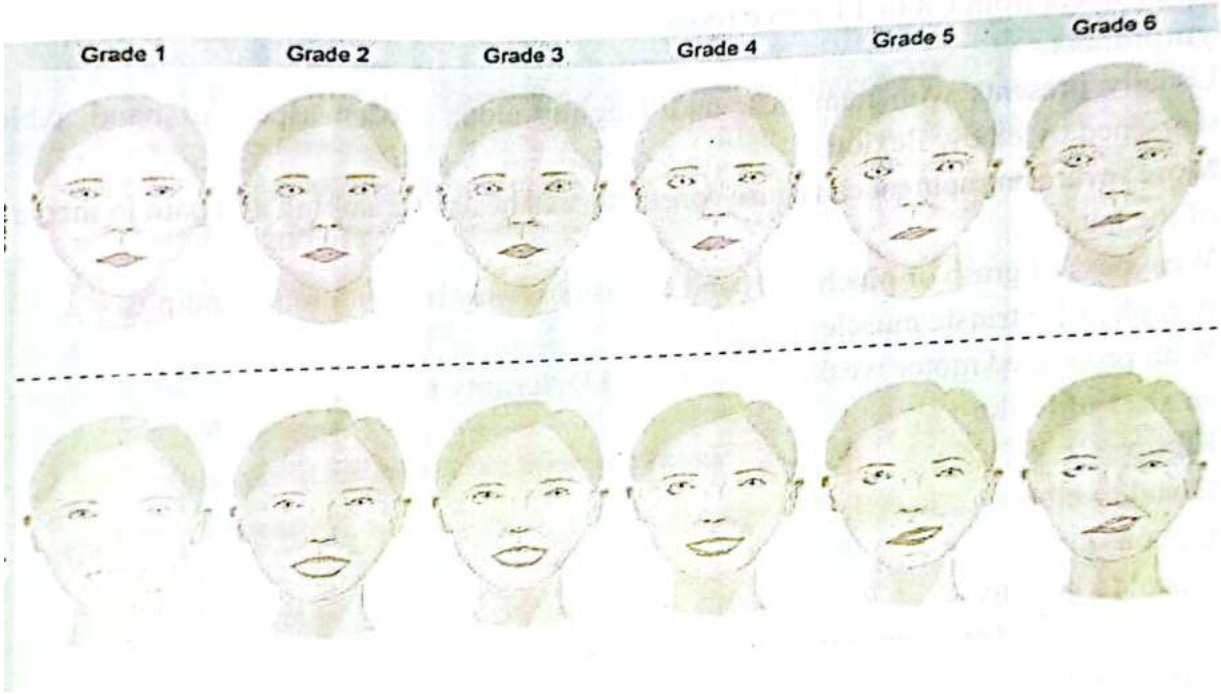
Grade	Description
I	Normal facial function
II	Mild Dysfunction—Slight weakness, slight synkinesis on close inspection. Moderate to good forehead function. Complete eye closure with minimal effort. Slight smile asymmetry with maximum effort. Normal symmetry and tone at rest.
III	Moderate Dysfunction—Obvious but not disfiguring difference between sides. Noticeable but not severe synkinesis. Slight to moderate forehead movement. Complete eye closure with effort. Strong but asymmetric smile with maximum effort. Normal symmetry and tone at rest.
IV	Moderately Severe Dysfunction—Obvious weakness and/or disfiguring asymmetry. Severe synkinesis. No forehead movement. Incomplete eye closure. Asymmetric smile with maximum effort. Normal symmetry and tone at rest.
V	Severe Dysfunction—Barely perceptible motion. Synkinesis usually absent. No forehead movement. Incomplete eye closure. Slight movement at the corner of mouth. Asymmetry at rest.
VI	Total Paralysis—No movement.

- Leukemia

Investigation :

1. MRI brain
2. CSF RE
3. NCS/EMG
4. ESR, CRP

Scanned with CamScanner



reatment

1. **Glucocorticoids**
   - Oral glucocorticoid for all patients
   - Early treatment increases rate of recovery
   - Usually treatment started if presentation within 7 days
   - Prednisone 60 to 80mg/day for 1 week without tapering.
2. **Antiviral therapy for severe palsy**
   - Valacyclovir 100mg TDS for 1 week
   - Acyclovir 400mg five times a day for 10 days.
3. **Prevent corneal injury**
   - Artificial tears
   - Ointment and taping

Scanned with CamScanner

NERVE PALSIES OF THE UPPER LIMB

Ulnar Nerve Palsy:

Composes of fibers from C8 to T1 nerve roots

Signs/Symptoms :

1. Usually presents with numbness and Tingling along medial aspect of hand, which is worsened by elbow flexion.
2. More severe entrapment can cause constant paresthesias , cramping and pain in medial side of the hand.
3. Weakness of grasp or pinch and hand clumsiness may be first motor findings
4. Atrophy of intrinsic muscles can occur
5. With prolonged motor weakness claw hand Deformity may form .

Common sites of lesion :

1. Elbow
2. Distal to elbow
3. Guyons canal
4. Distal to guyons

Common causes of ulnar nerve palsy :

Lesions at the elbow:

- Arthritis
- Fractures
- Compression during GA
- Compression by fibrous arch of flexor carpi ulnaris.

Lesion at wrist:

- Ganglion
- Tumour
- Fracture
- Aberrant artery

Mononeuritis Multiplex.

Sites Of Lesions

1. **Elbow**
    - **Wasting:**
      Wasting of hypothenar eminence and interosssei
      Ulnar border of forearm.
    - **Weakness**
      Finger abduction and adduction
      Flexion of 4^{th} and 5^{th} MCP joints
      Flexion of 4^{th} and 5^{th} DIP joints
      Ulnar Flexion of wrist
    - **Sensory loss**

Scanned with CamScanner

Ulnar distribution.

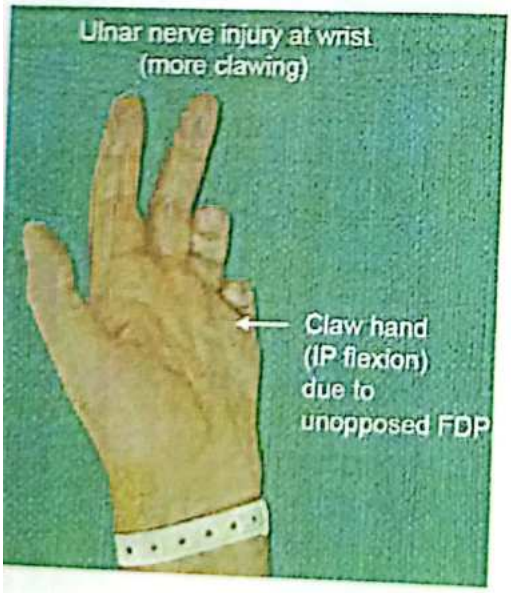
2. **Distal to elbow**
   - **Wasting**
     Wasting of only hypothenar eminence and interossei
   - **Weakness**
     Finger abduction and adduction
     Flexion of 4^{th} and 5^{th} MCP.
   - **Sensory loss**
     Ulnar distribution
3. **Guyons canal**
   - **Wasting**
     Hypothenar eminence and interossei
   - **Weakness**
     Finger abduction and adduction
     Flexion of 4^{th} and 5^{th} MCP
   - **Sensory loss**
     Palmar aspect of 5^{th} and medial aspect of 4^{th} Finger
4. **Distal to Guyons canal**
   - **Wasting**
     Hypothenar eminence and interossei
   - **Wasting**
     Finger abduction and adduction
     Flexion of 4^{th} and 5^{th} MCP
   - **Sensory loss**
     None

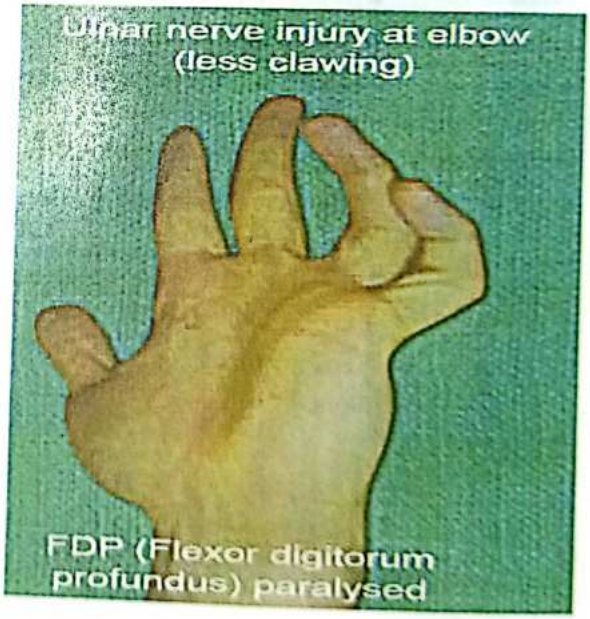
Scanned with CamScanner

Ulnar paradoxus

In proximal ulnar lesion (closer to the elbow), the Flexor Digitorum Profundus may also be denervated. As a result, flexion of the Interphalangeal joints is weakened, which reduces the claw-like appearance of the hand.

In distal lesion, at or below wrist
Condition of claw hand is worse because as FDP is spared ,there is active flexion of interphalangeal joint of medial two digits.This is called the **"ulnar paradox"** because one would normally expect a more debilitating injury to result in a more deformed appearance.





Treatment:

1. Mostly cases are treated conservatively
2. In most cases sustained elbow flexion and resting the elbow on hard surfaces such as desks are common precipitates of ulnar compression patients should avoid such activities
3. A short course of steroids followed by NSAID may be effective
4. If all conservative measures fail, ulnar decompression may be considered.

Scanned with CamScanner

Radial Nerve Palsy:

Originates from the posterior cord of the brachial plexus innervated by C5-T1.

Causes of RADIAL NERVE palsy:

1. **Axilla**
   - Trauma
   - Compression
2. **Spiral groove**
   - Trauma
   - Compression
3. **Proximal forearm**
   - Trauma
   - Subluxation of radius
   - Ganglion
   - Tumours
   - Elbow synovitis
4. **Wrist**
   - Trauma
   - Compression due to tight watch or bracelet

Sites of lesions:

Axilla:

Affects the following :

1. Wrist and finger extension
2. Forearm supination
3. Elbow extension
4. Sensory loss over the posterior forearm and over the triceps and first dorsal interossei.

Spiral groove:

Affects the following

1. Wrist and finger extension
2. Forearm supination
3. Sensory loss over 1st dorsal interossei

Proximal forearm

Affects the following

1. Wrist and finger extension
2. No sensory loss

Wrist:

The Sensory branch of the radial nerve becomes superficial at the Wrist

Scanned with CamScanner

Affects only Sensory loss over first dorsal interossei.

Treatment:

1. Conservative management is usually the best approach to one time damage to the nerve usually due to Saturday night palsy
2. Wrist splinting, physical therapy and pain management are also crucial.

Median nerve palsy:

Arises from lateral (C6 -C7) and medial cords (C8-T1) of the brachial plexus.

Compression may occur at:

1. Median mononeuropathy at the Wrist (Carpal tunnel syndrome)
2. Median neuropathy at Elbow.

Carpal Tunnel Syndrome :

Signs/ symptoms:

1. Numbness and pain in first three digits
2. Exacerbations of symptoms by manual activity.
3. Difficulty with fine manual tasks
4. Weakness of thumb abduction and opposition
5. Atrophy of thenar muscles.

Causes of Carpal tunnel syndrome:

1. Acromegaly
2. Hypothyroidism
3. Rheumatoid arthritis
4. Trauma
5. Amyloidosis
6. Gout
7. Diabetes
8. Pagets disease
9. Chronic renal failure

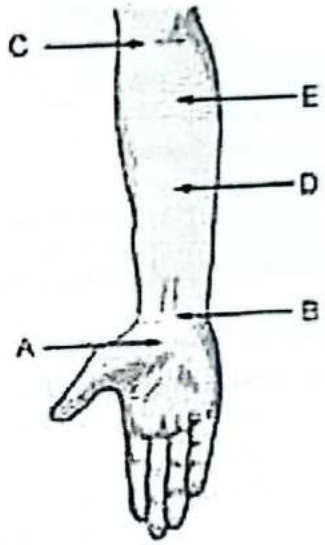
Treatment of carpal tunnel:

1. Splint Wrist in 30 degree extension
2. Local steroid injection
3. Diuretics
4. Carpal tunnel decompression

Scanned with CamScanner

Median nerve: common sites affected

(A) In the carpal tunnel (e.g. carpal tunnel syndrome, and some fractures and dislocations about the wrist).
(B) At the wrist (e.g. from lacerations).
(C) At the elbow (e.g. after elbow dislocations in children).
(D) In the forearm (anterior interosseous nerve) from forearm bone fractures, or by a tight tissue band at the origin of the superficialis.
(E) Just distal to the elbow, in the pronator teres nerve entrapment syndrome

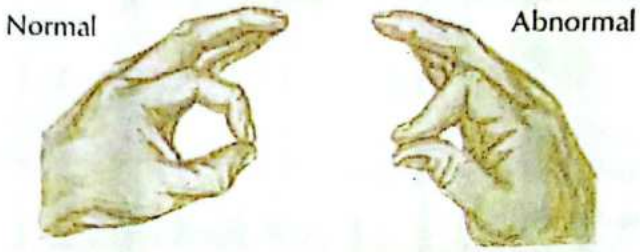


Pronator syndrome:
This is due to compression of the median nerve as it passes through the head of the pronator Teresa muscle just distal to elbow. It presents with pain on the Volar surface of the forearm following sustained Pronation of the forearm.

Anterior interosseus nerve palsy
This can be by entrapment by the fibrous band between the deep head of the pronator and flexor digitorum superficialis, overuse of the forearm and trauma. It presents as weakness of the index finger and thumb there are no sensory signs.

Scanned with CamScanner

Anterior interosseous syndrome



Hand posture in anterior interosseous syndrome due to paresis of flexor digitorum profundis and flexor pollicis longus mm.

Common Peroneal Nerve Palsy/ Foot Drop:

CAUSES:

1. Compressive disorder:
   Most common at the level of the fibula head due to the prominence of bony prominence at fibular head with frequent tethering of nerve by peroneus longest tendon. Other causes may include lumbar disc herniation and spinal stenosis.
2. Traumatic injuries :
   Severe ankle inversion, Fractures, Blunt trauma
3. Compartment syndrome
4. Iatrogenic
   Due to surgical procedures or protracted position in anesthesia.
5. Neurological disorders:
   Charcot Marie tooth disease and long standing diabetes.

Diagnosis:

1. Extremity imaging (plain X-ray or CT scan) MRI Lumbar spine , knee or ankle
2. NCS/EMG

Scanned with CamScanner

Difference between Common peroneal nerve VS L5 radiculopathy

	Common peroneal nerve palsy	L5 root lesion
Ankle inversion	Spared	Affected
Hip abduction	Spared	Affected
Straight leg raising test	Negative	Positive
Sensory loss	Lateral calf and dorsum of the foot	Lateral calf and dorsal of the foot , further proximally up to the lateral side of the leg
Pain	Usually painless	Often producing pain down the posterolateral aspect of leg.

Treatment :

1. For nerve transection, (traumatic or Iatrogenic) surgical nerve reconstruction should ideally occur within 72 hours.
2. For other etiologies, treatment is usually conservative due to the fact that partial or complete resolution of symptoms may occur spontaneously over time.
3. For nerve compression, nerve decompression and neurolysis should be performed. Nerve transfer , tendon transfer and combined procedures may play important part.

Cervical Spondylitic Myelopathy :

Refers to a progressive degerativs process affecting the cervical vertebral bodies and intervertebral disc's leading to the narrowing of Central spinal canal if sufficiently severe the cervical spinal cord is compressed causing cervical myelopathy.

Signs And Symptoms :

1. Pain In Shoulders , Subscapular Region
2. Numbness, Paresthesias
3. Gait Disturbance Usually Spastic
4. Sensory Deficits Usually Related To Dorsal Column Functions
5. Weakness In Lower Extremities With UMN Pattern.
6. LMN Findings In Upper Extremities C5 To C7 Myotomes Are Affected
7. Bladder Dysfunction /Urgency
8. Lehermitte Sign

Diagnosis :

1. MRI / CT with myelography
2. EMG/ NCS

Treatment :

Surgical decompression

Non -surgical:

1. Cervical immobilization
2. Restriction of high risk activities
3. NSAIDS, Muscle relaxants

Scanned with CamScanner

CEREBELLOPONTINE ANGLE TUMOUR: (CP angle Tumor)

Causes of CP angle lesion:

1. Acoustic neuroma
2. Meningioma
3. Cholesteotoma
4. Hemangioblastoma
5. Medulloblastoma
6. Basilar artery aneurysm

Clinical involvement :

Cochlear nerve:

95 percent of the patients major symptoms are hearing loss and Tinnitus. Chronic hearing loss in average duration of 4 years

Vestibular nerve:

Have unsteadiness while walking which was mild to moderate.

Trigeminal nerve:

Facial numbness, hypesthesias, pain

Abducent nerve

Impair abduction of the eye

Facial nerve:

Facial parents and taste disturbance

While large CP tumor may also involve last four cranial nerve as well

Diagnosis:

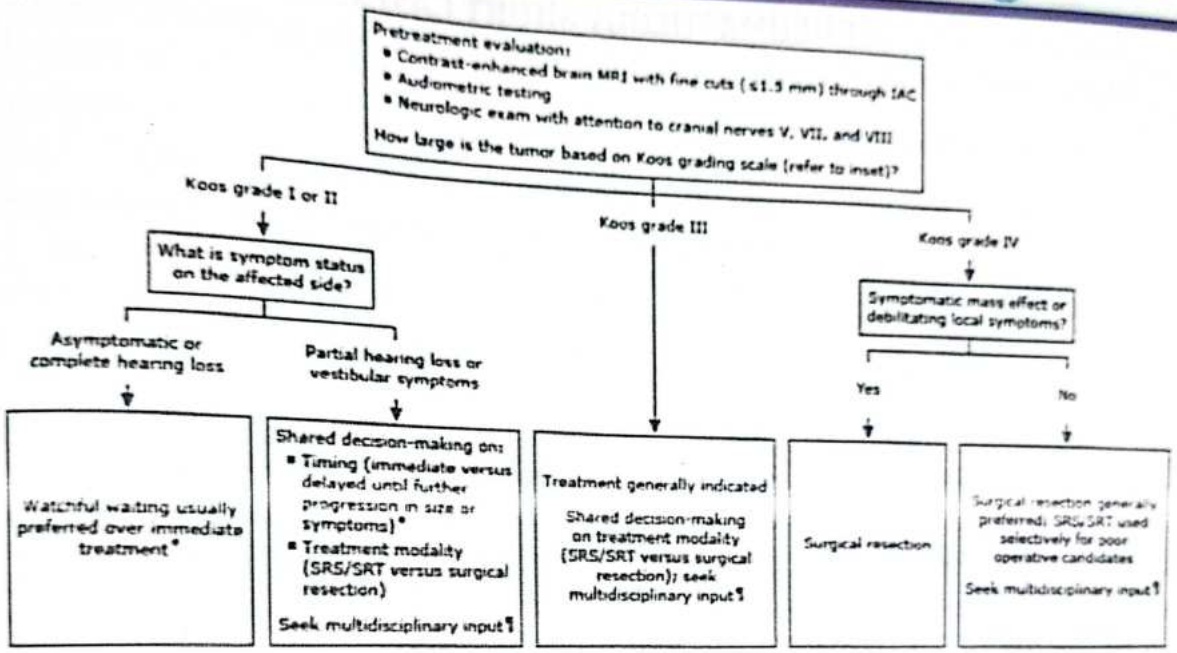
1. Examination
2. PTA
3. CE MRI Brain

Treatment

Surgical excision

Stereotactic radiotherapy

Scanned with CamScanner


Pretreatment evaluation:
• Contrast-enhanced brain MRI with fine cuts (≤1.5 mm) through IAC
• Audiometric testing
• Neurologic exam with attention to cranial nerves V, VII, and VIII
How large is the tumor based on Koos grading scale (refer to inset)?
Koos grade I or II
Koos grade III
Koos grade IV
What is symptom status on the affected side?
Asymptomatic or complete hearing loss
Partial hearing loss or vestibular symptoms
Symptomatic mass effect or debilitating local symptoms?
Yes
No
Watchful waiting usually preferred over immediate treatment*
Shared decision-making on:
• Timing (immediate versus delayed until further progression in size or symptoms)*
• Treatment modality (SRS/SRT versus surgical resection)
Seek multidisciplinary input¶
Treatment generally indicated
Shared decision-making on treatment modality (SRS/SRT versus surgical resection); seek multidisciplinary input¶
Surgical resection
Surgical resection generally preferred; SRS/SRT used selectively for poor operative candidates
Seek multidisciplinary input¶

Koos grade

Grade	Description
Grade I	Small intracanalicular tumor
Grade II	Small tumor with protrusion into the cerebellopontine angle; no contact with brainstem
Grade III	Tumor occupying the cerebellopontine cistern with no brainstem displacement
Grade IV	Large tumor with brainstem compression and cranial nerve displacement

IAC: internal auditory canal; MRI: magnetic resonance imaging; SRS: stereotactic radiosurgery; SRT: stereotactic radiotherapy.

Scanned with CamScanner

A. Examination of Hands:

- It consists of four steps i.e.; LOOK, FEEL ,MOVE & SPECIAL TESTS
- Before starting the examination, ask patient to up roll their sleeves up to elbows and place the hands of patient on a pillow.

2. Inspection:

Dorsal Surface:

- Inspect DIPs, PIPs, MCPS, wrists for
- any swollen erythematous joints (if present remember the hand and finger) ,
- Tapering of fingers (sclerodactyly)
- deformities (swan neck, button hole , Z deformity , ulnar deviation, subluxation at MCPs, dinner fork deformity at wrists) ,
- nodes (Herberdon nodes at DIPs, Bouchard nodes at PIPs)
- Rash overlying joints (PIPs, MCPs) (Gottron's papules)
- Wasting of dorsal interrossei muscles
- Nails (nail ridges and pitting, Onycholysis to rule out psoriatic nails) , periungal erythema ( ), splinter haemorrhages (Infective endocarditis in setting of SLE) , clubbing (in setting of RA related ILD)

Palmar Surface:

Inspect for

- FISSURINg rash (mechanic's hands suggestive of anti-synthetase antibody syndrome)
- Hypothenar and thenar wasting ,
- Palmar erythema , Dupuytren's contractures
- Scar at wrist may show previous surgery done for Carpal tunnel syndrome ,
- Finger tips for gangrene (dry or wet) , ulcers , pitting (shows old healed ulcers) , active Raynaud's phenomenon ,

Ask the patient to flex their elbows and examine extensor surfaces for rheumatoid nodules and psoriatic patches

Palpation:

Dorsal Surface:

- Ask patient if they have pain in any joints
- Start palpation by comparing temperature above and below the wrists
- Assess for tenderness of joints , start from wrists (examine with both thumbs) followed by MCPs, PIPs , DIPs (four fingers method)
- Assess for skin thickening (difficult to pinch in Scleroderma) , paper thin skin (Cushing's Syndrome)

Scanned with CamScanner

Palmar Surface:

Palpate radial pulses bilaterally (assess for radio-radial delay, rate, rhythm (conduction blocks are common in RA)

3. Movements:

Active Movements:

- Ask patient to perform adduction , abduction , opposition of fingers
- Extension and flexion at wrist joint

Movements against Resistance:

- Examine for opposition, abduction of fingers against resistance applied by examiner's fingers
- Examine for adduction of fingers against resistance by placing card between fingers
- Examine for pincer grip and hand grip
- Examine for wrist extension & flexion against resistance

5. Special Tests :

- **Prayer sign** : Patients with deformities secondary to RA or diabetic Cheiroarthropathy may not be able to perform it
- **Reverse Prayer or Phalen's sign:**

Ask patient to hold their arms for 30-60 seconds in front of them with wrists flexed pointing downwards; if patient feels tingling sensation along distribution of median nerve, Phalen's test is said to be positive

- **Tinel's s** : Tap with finger on flexor retinaculum
- **Function capacity** : ask the patient to unbutton his shirt's button or give key to the patient and ask him to act as if he is trying to unlock the lock (Key in a lock test)

Relevant Examination:

If deformities are suggestive of RA, in relevant examination look for signs of

- red eyes(episcleritis),
- auscultate bases of chest for ILD and heart for conduction abnormalities & murmurs
- Examine abdomen for splenomegaly (Felty's syndrome) ,
- Look for pedal edema (amyloidosis)
- Look for hidden psoriatic patches behind the ears, on scalp, umbilicus, and knees if DIP involvement is observed during examination.

B. Examination of Back (Case of Ankylosing Spondylitis [As])

Adequate exposure, politely ask (male) patient to remove the shirt

2. Inspection:

Scanned with CamScanner

Look for gibbus formation, kyphosis, scoliosis, rash, or psoriasis.

In context of AS, look for **question mark sign** (occurs in advanced disease due to combination of thoracic hyperkyphosis, loss of lumbar lordosis, neck flexion deformities)

Gait should be assessed.

2. **Palpation:**

Examine for vertebral tenderness (with fist)

Range of Motion:

Cervical spine: Flexion and extension and lateral rotation

Thoracoumbar spine: Assess forward flexion, backward flexion and lateral flexion

Specific Tests:

- **Wall to Occiput distance:** with patient's heels and buttocks touching the wall, measure distance between wall and occiput of patient (normal= 0 to 2 cm)
- **Wall to tragus distance** : (normal = below 10 cms)
- **Chest expansion** : reduced in AS
- **Modified Schober's test:** Mark one point at the level midway between two PSIS and other 10 cms above it. Ask patient to bend forward without bending their knees, measure the distance by standing behind when patient is bent forward. If it's less than 15 cm, it is said to be positive.
- **Finger to floor distance:** Measure distance between middle finger of patient and floor with patient standing against the wall in neutral position .With patient maximally bent laterally, again measure distance between middle finger and floor (distance between both positions = > 10 cm)
  - Ask patient to lie on the examination couch and examination for any peripheral joint swelling (especially knees, ankles), tenderness at sites of Achilles tendon insertion and in heels for plantar fasciitis.
  - In relevant examination,

Auscultate apices of lungs for apical fibrosis and precordium for murmur of AR

Examine eyes for any redness secondary to uveitis and hands and feet for dactylitis.

C. Knee Examination:

(Case of knee swelling)

1. Inspection:

From front, side and back (to look for associated Baker's cyst) in standing position

Look for erythema, bogginess, asymmetry, scars, and psoriatic patches

2. Palpation: (in lying position)

- Examine for temperature differences (at knees , above and below knees) and compare with other side if only one knee is swollen
- Palpate in popliteal Fossa for Baker's cyst

Scanned with CamScanner

- Tenderness should be checked along joint line (medial and lateral joint lines) and at the sites of bursae (suprapatellar, infrapatellar, prepatellar and pes anserine bursa sites in suspected bursitis)
- Patellar tap (a tap is felt on palpating patella ; positive in case of effusion)
- Bulge sign (with one hand, effusion is redirected to other side and felt as a bulge on the other side)

3. Movements:

- Check range of motion and if movements are painful or not while performing flexion and extension
- Examine for crepitus

4. SPECIAL Tests:

Anterior drawer test: for assessment of Anterior cruciate ligament integrity

To perform the anterior drawer test in supine position, patient's hip should be at 45 degrees and patient's knee at 90 degrees of flexion. You can fixate this position by gently sitting on the foot of your patient. Then palpate the joint line with your thumbs, and try to move the tibia anteriorly in an explosive movement. This test is positive if the tibias translates anteriorly more than 6 mm or if you experience a soft end feel.

Posterior drawer test: for assessment of posterior cruciate ligament integrity

To conduct the test, the patient is in supine lying position with the hip in 45° and the knee in 90° of flexion. The examiner then palpates the joint line with his thumbs while grabbing onto the tibia from anteriorly. The examiner then translates the tibia posteriorly in an explosive movement

Positive Outcome. Soft end-feel or increased posterior translation on the tested knee compared to the other knee

- Examine one joint above (hip joint) and one below the knee (ankle) to look for signs of swelling range of motion

D. General Physical Examination:

Usually comes in the setting of SLE, Systemic Sclerosis or Myositis

If the command is GPE,

Start with vitals (BP should not be missed considering Lupus nephritis and Scleroderma renal crisis) followed by examination of hands (as mentioned in examination of hands)

In case of suspected SLE

- look for signs of alopecia (scarring / patchy) ,
- Face for malar or discoid rash , oral ulcers (palatal ulcers are more specific for SLE) ,

Scanned with CamScanner

- Cushingoid features (iatrogenic) , proximal myopathy
- Auscultate for pleural effusion and pericardial effusion (serositis)
- Examine abdomen for organomegaly
- Look for pitting pedal edema
- Communicate with patient to assess orientation and examine cranial nerves (to rule our neuro-psychiatric SLE)
- Fundoscopy (for optic neuritis, hypertensive retinopathy)

In patients of Scleroderma

- Assess skin thickness by pinching patient's skin between thumb and index finger,
- Assess extent of skin involvement { limited scleroderma if distal to elbows and knees , diffuse scleroderma if proximal to elbows and knees and truncal involvement} ,
- Look for ulcers, gangrene, auto amputated digits , Raynaud's phenomenon, sclerodactyly
- Hypertension and Pitting edema, signs of malignant hypertensive retinopathy on fundoscopy { in case of renal crisis}
- Look for decreased oral aperture and peri-oral furrowing due to skin thickening along with prominent nose
- Telangectasias are usually present on hands, face ,tongue and chest
- Chest should be auscultated for features of ILD (end inspiratory bibasal crackles)
- Precordium should be auscultated for loud P2 secondary to Pulmonary arterial hypertension
- Abdominal examination to be done for any signs of pseudo-obstruction and small intestinal bacterial overgrowth (hypermobile gut)

{Asking the patient to put three fingers in mouth, commenting on nose as beaked nose or fish mouth should be avoided as this is considered disrespectful for the patients and is obsolete }

INFLAMMATORY MYOSITIS:

In patients with suspected myositis (dermatomyositis and polymyositis),

Skin features that should not be missed include:

- Gottron's papules : erythematous macular rash over PIPs and/or MCPs
- Gottron's Sign : erythematous rash over elbows
- Heliotrope rash: violaceous rash over eyelids
- Malar rash : doesn't spare nasolabial folds in contrast to SLE
- Shawl sign : over upper back and shoulders
- V sign : hyperpigmentation over upper chest and neck
- Mechanic's hands : cracking fissuring rash on palms
- Raynauds phenomenon
- Power of Proximal muscles of both upper and lower limbs and neck flexors should be assessed

Scanned with CamScanner

- Chest should be auscultated for ILD
- Lymphadenopathy should be assessed as dermatomyositis is associated with high risk of malignancies

VASCULITIS:

In case of suspected vasculitis, after doing GPE (in both long and short case) ,

- Examine all possible pulses(bilaterally)
- Start with palpating Radial pulses bilaterally (compare volume and if one feeble or completely non-palpable) , followed by Brachial pulses , take BP on both arms , move on carotid and subclavian pulses , palpate temporal arteries bilaterally (at temples, carefully palpate for diminished pulsation on one side & cord like sensation (in Giant cell arteritis)
- Palpate for bilateral femoral arteries followed by popliteal and posterior tibial & dorsalis pedis arteries to complete lower limbs arterial examination.
- Auscultate for bruits over carotid and temporal arteries and for abdominal aortic aneurysm
- Auscultate precordium for murmurs
- Examine for stiffness and weakness of hip and shoulder girdles (Polymyalgia rheumatica)
- Examine for neuropathies (foot drop, wrist drop; common in Polyarteritis nodosa & Eosinophilic granulomatosis with polyangiitis)

Scanned with CamScanner

LONG CASE SCHEME OF RHEUMATOLOGY CASE :

Since most of the patients of rheumatology have arthritis and arthralgias (irrespective of the diagnosis), and if patient gives history of arthritis,

After vitals and GPE, examination should start with **musculoskeletal system**

- Start with the affected joints (e.g hands in case of RA, knees or ankles in case of AS) And then move on the hands (if they were not examined first) followed by wrists, elbows, shoulders
- Then ask patient to lie down and examine hips, knees, ankles
- (Check swelling ,tenderness,deformities,contractures, Range of motion/movements in all joints in a systemic way)
- Gait should be examined too along with back examination (mentioned in Scheme of back examination) if patient has history suggestive of AS (Inflammatory lower backache with early morning stiffness)

- After completing musculoskeletal examination, proceed as per other complaints of patient.
- Skin findings should not be missed
- All systems, however should be examined as rheumatological diseases can manifest with multi-systemic involvement

- **CNS**: Tone, power, reflexes, plantars, sensations , cranial neuropathies (rule out CVA , demyelinating disorders, neuropathies)
- **CVS** : examine for conduction blocks, murmurs , loud P2
- **Chest** : apical fibrosis (AS), ILD (RA, Scleroderma) , Pleural effusion (SLE serositis)
- **Abdomen**: visceromegaly , gut motility , aortic aneurysms (vasculitis)

Complete with **fundoscopy**:

- Look for uveitis, Iris nodules (RA) ,
- pale disc (optic neuritis in SLE associated NMOSD, MOGSD) ,
- flame shaped haemorrhages and cotton wool spots (lupus nephritis, scleroderma renal crisis)

Scanned with CamScanner